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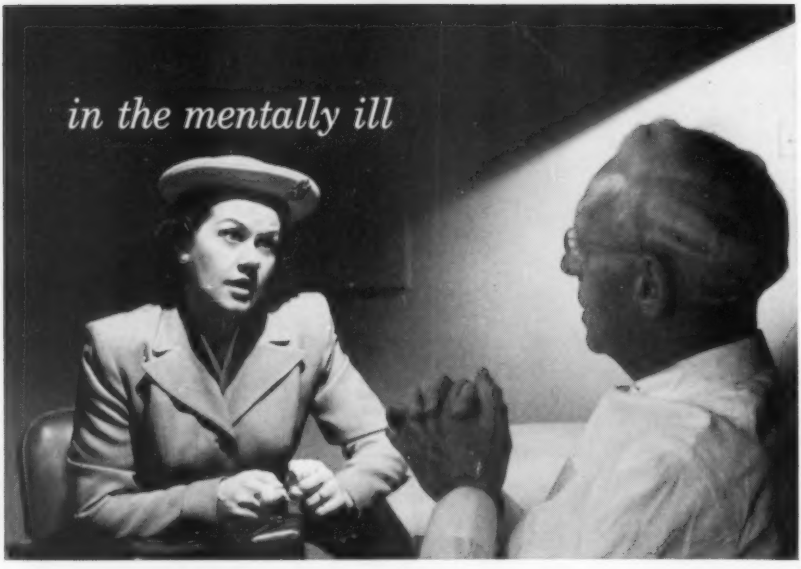

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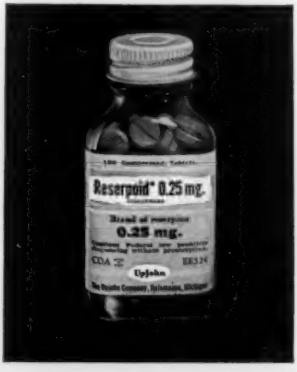

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1. Howell, T.H.; Harth, J.A.P., and Dietrich, M.: Practitioner *173*:172.
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Volume 6 Neurology *Number 1*

Protrusions of Thoracic Intervertebral Disks

Kenneth H. Abbott, M.D. and Richard H. Retter, M.D.

UNFORTUNATE EXPERIENCES previously reported with protrusions of the thoracic intervertebral disk have led to a hopeless therapeutic attitude toward these lesions. More recent reports and experience of the authors suggest that this opinion is not entirely justified. Most of the grave sequelae following laminectomy have arisen out of 1) tardiness of the operation, 2) technical problems in an area of anatomic disadvantages, and 3) the midline location of the disk protrusions. More recently it has been observed that "laterally placed" disk protrusions have been mistaken for angina pectoris, intractable abdominal pains, and intercostal neuralgias, among other diagnoses, and multiple abdominal, cardiac, and other operations have been performed. Furthermore, not a few of the "midline" thoracic disk protrusions have given rise to neurologic symptoms of either a radicular or long-tract-sign nature or both for weeks to several years; thus, these might well have been studied earlier and come to surgical exploration before advanced degenerative alterations in the spinal cord and nerve roots had taken place. When the latter situation has occurred, it is true that the spinal cord is vulnerable to the slightest untoward manipulation and there is great hesitance to attempt surgery on these lesions.

In the cases presented herein, patients experienced various back, shoulder, arm, chest, and abdominal pains. Some were thought to have cardiac, pulmonary, and various types of abdominal disease. One very neurotic individual became addicted to narcotics after psychotherapy had failed to give her relief from pain. A similar situation arose in a nurse who was considered to have a hysterical re-

From the department of surgery, division of neurosurgery, Ohio State University College of Medicine, Columbus.

Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 29, 1955.

TABLE 1

RESUME OF 10 CASES OF THORACIC INTERVERTEBRAL DISK PROTRUSIONS

Case Number	*Sex*	*Age*	*Level*	*Position*	*Duration of symptoms*	*Result*
1.	M	22	T10	Lateral (arachnoiditis)	10 months	Fair–
2.	F	33	T11	Lateral	4 years	Good
3.	M	61	T1	Lateral	10 days	Excellent
4.	F	24	T5	Lateral	3 months	Excellent
5.	F	26	T10 & 11	T10 central T11 lateral	5 months	Good
6.	M	41	T12	Centrolateral	11 months	Fair
7.	F	43	T11 & 12	T11 lateral T12 centrolateral	6 months	Excellent
8.	M	40	T9	Central	1 year	Fair–
9.	M	44	T6	Central	years? 6 months (def.)	Poor
10.	M	49	T11	Central	several months	Death–pulmonary embolism

tention of urine. In this group were six laterally placed disks and two centrolateral disks. Two patients had two disk protrusions each. Most of these patients made a good or excellent postoperative recovery (table 1).

Epstein[1] has emphasized that overlooking these lateral disk protrusions is understandable because of 1) the paucity of neurologic deviations from normal, and 2) the lack of possible awareness of the lesion in the absence of neurologic deficit. To this might also be added the general belief of unreliability of minor defects in the Pantopaque column in the thoracic region. The intercostal neuralgias have also been a surgical disappointment to the surgeon as well as the neurologist, since in previous years reports were made of negative explorations and failure to relieve pain by intradural posterior rhizotomy. However, it is increasingly evident that a few of these patients do have protruded thoracic disks which are laterally placed and, if treated surgically, they will respond satisfactorily.

REPORT OF CASES

Case 1.—A 22 year old man had complained of pain in the lower back, left hip, ventral thigh, and lower left abdomen since lifting a 100 pound bag of feed. When seen ten months after the incident he also had weakness in the left lower extremity, with mild sensory deficit up to L2, rather severe saddle hypesthesia, and complete impotence. The deep tendon reflexes were all hyperactive. A Pantopaque myelogram diclosed an irregular filling defect at T10. At operation this proved to be due to a T10 left lateral disk protrusion associated with severe focal arachnoiditis from T9 to T11. Removal of part of the involved arachnoid and the disk protrusion was accomplished. When last heard from two years later the patient was working and relatively free from pain, but the sensory deficit and increased tendon reflexes persisted.

Case 2.—A 33 year old woman was seen in 1949 because of bouts of left thoracoabdominal pain present since an injury in 1945. She had become addicted to opiates, making evaluation difficult, particularly so since she also had severe right flank pain. She walked with a limping gait (left), her back movements were severely restricted, Lasegue's sign elicited pain on the left, and the deep-tendon reflexes were hyperactive in both lower extremities. Vague sensory changes were noted corresponding to a bilateral sensory level of about L1 dermatome. A Pantopaque myelogram (figure 1) disclosed

a constant defect between T11 and 12 on the right. The cerebrospinal fluid contained 60 mg. per cent total protein. At operation a large laterally placed prolapse of the nucleus pulposus was removed from the right side (T11). She made a good recovery after psychiatric care was instituted for neurosis and narcotic addiction.

Case 3.—A clothing merchant, age 61, had a rather sudden onset of upper dorsal back pain about March 10, 1953. The pain was constantly present but more severe at night, so that he was unable to sleep unless he sat up. At first he was considered to have anginal pain. In the week previous to examination on March 20 he had noted radiation of the pain into the right scapula, then into the medial aspect of the arm and forearm, with paresthesia in the fourth and fifth fingers (right). Coughing, sneezing, and straining further aggravated the pain, but it was not affected by movement of the head and neck. There was no history of trauma. The deep tendon reflexes were unaltered. There was slight(?) weakness of the right fourth and fifth fingers. Percussion in the right upper dorsal paraspinal area elicited the pain and paresthesia described above.

A myelogram (figure 2) demonstrated a constant filling defect between T1 and 2 on the right side. At operation (partial hemilaminectomy) a fair-sized laterally placed T1 disk protrusion was removed. He made a rapid and complete recovery and in three weeks returned to his occupation.

Case 4.—Persistent left fifth intercostal neuralgia was experienced for three months by a 24 year old female. The pain was worse at night and was aggravated by cough, sneeze, and strain. She was thought to have some type of cardiac pain, but no roentgenographic or electrocardiographic changes were found. No neurologic changes were detected. A Pantopaque myelogram disclosed a small defect at T5 on the left. At operation (partial hemilaminectomy) a small laterally placed T5 disk was removed. There has been complete relief from the intercostal neuralgia. (A myelographic defect similar to the one seen in this case is seen in figure 3.)

Case 5.—A nurse, age 26, complained of severe low back and leg pains with marked weakness of her lower extremities and an atonic bladder. Her symptoms had begun five months before. Radicular pains in the right side of the abdomen (mid- and lower sections) had previously given rise to diagnosis of renal colic, colitis, and other visceral disease. An atypical cauda equina and conus medullaris compression syndrome was found—an atonic bladder with loss of bladder and rectal sphincter con-

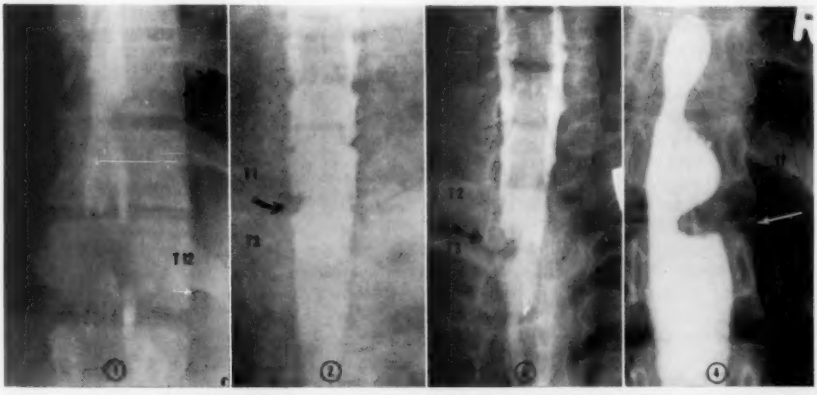

FIG. 1. A large extradural defect (constant at the midline and to the right) seen in the myelogram at T11-12 proved to be a protruded disk at T11 (case 2).
FIG. 2. Myelogram defect consequent to laterally placed T1 protruded intervertebral disk (case 3).
FIG. 3. A typical Pantopaque myelogram defect of a laterally placed (T2) protruded disk causing back and radicular pain (case 4).
FIG. 4. Pantopaque myelogram showing two persistent right centrolateral defects due to protruded disks, at T10 a right lateral protrusion and at T11 a midline protrusion (case 5).

trol, weakness in the lower extremities with decreased but intact tendon reflexes, positive Babinski signs, and irregular sensory loss up to T12 but with relatively intact sensation in the "saddle area." There was a partial subarachnoid block and the cerebrospinal fluid was slightly xanthochromic with a total protein of 30 mg. per cent. A history of back strain from lifting patients was elicited at a later date.

A myelogram (figure 4) disclosed a large midline defect at T11 and a smaller right lateral defect at T10. At operation these proved to be protruded disks and were removed without difficulty. Because of radicular pain the right posterior sensory root (T10) was sectioned. Her postoperative course was difficult and slow, being complicated by narcotic addiction in an individual with "extreme anxiety and depression in a neurotic personality showing obsessive and compulsive features." After a few months in a psychiatric sanatorium, she was able to return to nursing and is now director of nursing service in a small hospital. Minor neurologic deficits remain (decreased deep tendon reflexes and dysesthesia in the lower extremities).

Case 6.—A 41 year old man experienced acute lumbodorsal back pain in October 1952 while shoveling coal. Soon after the accident weakness of the legs appeared. The symptoms persisted in spite of a back brace. He was examined in September 1953; in the previous five months he lost 30 pounds in weight, his legs became moderately weak, he experienced some mild difficulty in the control of his urine, and he noticed the lack of sweating on the left side of his head and face. On examination he presented an emaciated appearance, an unexplained left Horner's syndrome, marked spasm of the back muscles, and tenderness to percussion over the spinous processes of T11 and 12 and L1 and in the right paraspinal area. The tendon reflexes in the lower extremities were decreased but equal. There were no demonstrable sensory changes, but there was evidence of mild urinary retention. A myelogram disclosed a nearly complete block at L1 to T11, and the cerebrospinal fluid contained 66 mg. per cent total protein. A bilateral laminectomy (T11 to L1) revealed a large right centrolateral disk protrusion at T12. The dentate ligaments of the cord were severed and the protruded disk mass was removed. His postoperative course showed a slight increase in the lower extremity weakness and the sphincter disturbance persisted. A myelogram performed March 31, 1954 revealed an irregular defect at T12 suggestive of arachnoiditis.

When examined one year later, September 15, 1954, he was unable to work and complained of back and right leg pain and cramping in the right foot. On examination the tendon reflexes in the lower extremities were moderately hyperactive but equal; there were no pathologic great-toe signs; there were irregular subjective sensory changes in both lower extremities, more so on the right. He had no urinary bladder or sphincter trouble. In April 1955 he was only slightly improved.

Case 7.—A 43 year old woman complained of severe thoracic and lumbar back pain and burning paresthesias in the right lower extremity of six months' duration, with a weight loss of 61 pounds. One year previously protruded disks had been removed successfully from L5 and L4 interspaces and she had returned to work. After two months of unsuccessful conservative management, she was examined and found to show decreased appreciation of tactile, pain, and temperature sensations in the lower extremities (right greater than left), with hyperactive deep tendon reflexes (left greater than right) and a positive Lasegue's sign (right). Stress incontinence was occasionally noticed. A myelogram disclosed a moderate filling defect at T12 on the right and a small lateral defect at T11. At operation a moderate-sized soft protrusion centrolaterally located at T12 was removed and a small laterally placed disk at T11 was encountered and removed. A four-year follow-up disclosed a complete recovery without residual neurologic deficit.

Case 8.—A 40 year old male laborer complained of severe back and bilateral leg pains after injury to his back one year previously. He had had several minor back injuries. Gradual increase in inability to walk appeared associated with sphincter disturbances. He had consulted a surgeon ill-equipped to handle the problem. A myelogram was performed showing a large defect in the midline at D9. An operation performed elsewhere failed to disclose the lesion, but subsequent roentgenograms have shown that the procedure was performed at T11. His symptoms persisted. A sensory level of mild intensity at L1 to T12 with bilaterally hyperactive reflexes and positive Babinski signs were noted. He was partially disabled but

could walk and do light work. He is fearful of further surgery so has remained at home for the past 11 months without serious progression of his neurologic deficit until recently, when his condition has shown further deterioration so that he is now bedridden and in severe pain.

Case 9.—A 44 year old farm hand complained of backache for several years, which had been acute and associated with paresthesia in the legs and feet for six months. In the previous week ascending sensory and motor paralysis with loss of sphincter control and atony of the bladder developed. On examination a paraplegia in extension was found with a sensory level at the T8 dermatome. A myelogram revealed an incomplete midline block at T6 and the cerebrospinal fluid contained 110 mg. per cent total protein. At operation the spinal cord was pale, thinned, and acutely angulated posteriorly at T6. A transdural approach was used to remove a large central prolapse of the nucleus pulposus. He failed to show any improvement after seven years.

The following case is reported through the courtesy of Dr. H. E. LeFever. Another of his patients, who had a midline T4 disk removed over ten years ago, is also included in figure 5.

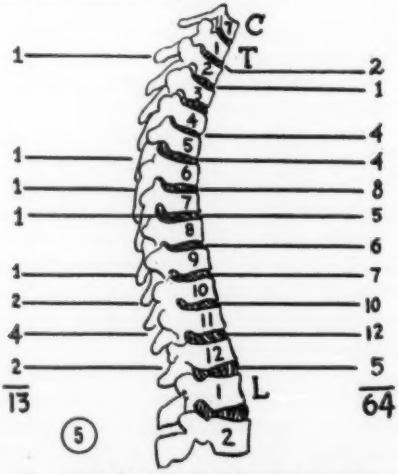

FIG. 5. The figures to the right record the site of the reported thoracic intervertebral disk protrusions, including those reported here. The 13 disk protrusions listed on the left are the authors' and include two cases with two disk protrusions each.

Case 10.—A 49 year old white male was admitted to the hospital in February 1955 because of back pain of several months' duration. He had shown rather advanced spinal osteoarthritis. After his dismissal from the hospital he began to experience pain radiating down the left lower extremity with increasing intensity. This was accompanied by difficulty in defecation and micturition. He emphasized that he required an enema to move his bowels and that he was having sudden bouts of urinary frequency. He was no longer able to walk without crutches. Examination revealed marked bilateral weakness of the lower extremities with bilateral foot-drop. Although there was no disturbance in position sense in the lower extremities, there was a definite sensory level to touch, pain, and temperature at about T7 or 8. Bilateral Babinski signs were present and abdominal and cremasteric reflexes were absent. Lasegue's sign was negative bilaterally. A Pantopaque myelogram revealed severe osteoarthritic lipping involving most of the vertebral column, with a questionable midline defect at T10 and T11. The spinal fluid protein content was 50 mg. per cent. On March 24, 1955 a bilateral laminectomy at T10 and 11 was carried out, and at T11 a herniated intervertebral disk was encountered which was obviously compressing the spinal cord. The patient's postoperative course was uneventful until April 5, 1955, when he had a sudden, massive pulmonary embolism causing death.

DISCUSSION

This series is obviously too small for a statistical analysis, but it presents a few clinical points of interest. No age group appears to be favored, and sex or type of work does not appear to be a factor since women and men of both sedentary and active occupations were afflicted. The neurologic examination alone was of little or no value in the diagnosis of most cases, but the myelogram was of great value.* A correct diagnosis was made in seven out of nine

*It is true that in our hands atypical myelographic defects have proved on surgical exploration to be due to 1) localized arachnoiditis, 2) small cyst of the arachnoid, 3) osteoarthritic spur, and 4) "no pathology found."

cases. It is the authors' opinion that the surgical results could be improved if 1) earlier operation had been instituted, and 2) rhizotomy of the dorsal root compressed by the laterally placed disk protrusion had been performed in each instance. In most cases relief from radicular pains was obtained, except in the two patients who were narcotic addicts and in another patient who was operated on previously at the wrong level. The spinal fluid protein content was significant only when a complete or nearly complete block was present. Plain roentgenograms of the spine were not helpful in this series, even though degenerative and osteoarthritic changes were seen in an occasional case. Calcification of the intervertebral disk was not encountered in this group.

REVIEW OF THE LITERATURE AND ANALYSIS OF CASES

Incidence. The estimate by Love and Kiefer[2] that thoracic disk protrusions occur two or three times per 1,000 cases of disk protrusions seems to the writers and others to be too low. Logue[3] found a 4 per cent incidence (11 cases in 250), but he pointed out that this may be exaggerated due to the restricted choice of cases that were admitted to his hospital. Epstein[10] did not mention from how many disk protrusion cases his four thoracic disk protrusions were gleaned. The nine cases with 11 protrusions encountered in the writers' series of over 600 disk cases, an incidence of 1.5 per cent, is nearly ten times greater than incidence in the Mayo Clinic series. This suggests that the true incidence may be much greater than they have indicated and may also be related to the special character of their admissions.

A review of the literature up to December 1954 revealed a total of 51 thoracic disk protrusions reported, to which this paper adds 13 for a total of 64. The previously reported cases include: Elsberg, two;[4] Mixter and Barr, four;[5] Hawk, four;[6] Bradford and Spurling, one;[7] Love and Kiefer, 17,[2] including three lateral disk protrusions; Muller, four;[8] Logue 11;[3] Van Landingham, two protrusions in one case;[9] Svien and Karavitis, two protrusions in one case;[10] and Epstein, four.[1]

Site and position. Thoracic disk protrusions have been found at every level (from between T1 and 2 to T12 and L1) except between T3 and 4 (the T3 level); this is probably because the series is too small at the present time to be statistically significant. Figure 6 shows the disk levels at which protrusions have occurred; on the right side the figures denote the total number reported disks at each level, including this series (64 protrusions). On the left side the figures refer to the 13 disk protrusions in this series. In two cases (5 and 7) multiple disks were encountered at T10 and 11 and T11 and 12.

Haley and Perry studied 99 spinal columns at post mortem and found seven thoracic disk protrusions, 53 cervical disks, and 27 lumbar disks with multiple disk protrusions in the cervical and lumbar areas.[11] They and others have shown that disk protrusions and degeneration occur with greatest frequency where mobility of the spine is greatest, namely, the midcervical, lower thoracic, and lower lumbar areas.

Young called attention to degenerative disk disease in cervical and thoracic areas as a causative factor in disk protrusions in these areas.[12] Epstein[1] has emphasized the frequency of degenerative disk changes and protrusions at the eleventh thoracic interspace, and be-

lieves that both the mobility and degenerative disease at this site are factors in the relative frequency of disk protrusions here.

The clinical importance of differentiating between the central, or centrolateral, and laterally placed disks already has been emphasized. Love and Kiefer[2] noted this difference, but made no clinical interpretation of this point other than to state the number of protrusions in each group (11 midline, three centrolateral, and three lateral). Svien and Karavitis[10] reported a case with two disk protrusions, T1 and T2, which appear to have been lateral disk protrusions. Epstein reported three laterally placed disks out of four, and emphasized their clinical importance. All three were females in whom hysterectomy had been performed in one, a benign pericardial cyst was removed in another, and a contemplated exploratory laparotomy was averted in a third. The symptoms in each case with a laterally placed disk proved to be due to the nerve root compression, yet pyelograms, gastrointestinal and gallbladder roentgen studies, and uterine surgery had preceded even a suggestion of the neurogenic origin of the symptoms.

In the series reported here two patients had multiple thoracic disk protrusions (two each). Other thoracic multiple disk protrusions have been reported by Svien and Karavitis[10] at T1 and 2, and by Van Landingham[9] at T7 and 8; in the latter case they were associated with kyphosis dorsalis juvenilis (Scheuermann's disease). Thus, four cases with multiple thoracic disk protrusions account for eight of the total of 64 protrusions, or about 12.5 per cent disk incidence, a case incidence of 8 per cent.

Age and sex. Of the total thoracic disk protrusions reported, ages have ranged from 17 years[9] to 73.[2] In the authors' series there was a tendency for a high incidence at a younger age group than indicated in Logue's[3] review, wherein he showed the greatest number of cases to be in the 40 to 60 age group. Three of Epstein's[1] four patients were over 50 years of age, and one was 30 years old. In ten cases reported here, three were in the twenties (youngest 22), one in the thirties, five in the forties, and the oldest was 61. Laterally placed disks occurred in each of these age groups. Sex appears to play no role in their incidence since they are about equally divided between male and female.

Clinical symptoms. The symptoms of thoracic disk protrusions may be divided into three groups. 1) A group in which the long-tract signs appear as they do in spinal cord lesions, but with a tendency for more pain and paresthesia to appear both in the back and lower extremities. The paresthesia and pains are usually radicular in character, though occasionally difficult to recognize as such. In this group the lesion is a central disk protrusion with anterior compression of the spinal cord above the level of the conus. The course may be only a few weeks or up to 14 years.[3] When paraplegia appears, operative interference is usually unsuccessful. 2) In another group the central disk protrusion occurs in the T11 or T12 area and compresses the conus medullaris and cauda equina, giving rise to much back and lower extremity pain with loss of sphincter control, motor weakness in the sacral and lumbar segments, and saddle anesthesia with later involvement of lumbar dermatomes. Radicular pains in the T11 and 12 and L1 and 2 dermatomes are common, and sensory changes in these areas

sometimes may be detected quite early. 3) A third group has been emphasized in this paper – the laterally placed disks. In these cases there is early evidence of nerve root compression by a protruded intervertebral disk, with radicular pain and minimal or no sensory changes; signs of compression of the spinal cord are minimal or absent and if present are reversible. These laterally placed disk protrusions in the thoracic region appear to give rise to symptoms analogous to similarly placed lesions in the cervical region. However, these symptoms are more easily confused with visceral disease since the pains and paresthesia occur on the trunk. Not a few patients have had preceding or simultaneous back pain or ache, which deserves emphasis. Seldom is pain aggravated by back movements, though occasionally deep breathing, coughing, and straining elicit distress.

The differential diagnosis between visceral disease, spinal cord tumor, chronic back sprain, and these various thoracic disk protrusions is not an easy one. Probably the best three aids are 1) to think of the possibility of a thoracic disk protrusion, 2) do a careful neurologic examination, and 3) perform a careful Pantopaque myelogram with slow movement of the oil column in both oblique positions with roentgenograms taken of any suspicious area. We fully agree with Epstein's[1] suggestion that "cross-fire lateral views are of considerable help, frequently showing pooling of oil at this interspace where it collects in a pattern characteristic of a partial obstruction in the ventral quadrants of the spinal canal." Thoracic myelography is still a difficult procedure. We have used 9 cc. of Pantopaque as the contrast medium in most cases. In a few instances as much as 18 cc. has proved helpful in showing defects in the lateral thoracic areas. More recently 20 to 25 cc. has been advocated for complete spinal myelography.

Treatment. All except one of the patients in this series were benefited by surgery to a gratifying degree. The surgical technic involved need not concern us here except to indicate the need for wide laminectomy (facet included), with opening the dura in most of the central disk protrusions. It has been helpful to section the dentate ligaments in a few instances in order to lessen traction on the cord and to permit greater freedom of movement. Kahn[13] has implicated the dentate ligaments in stress analysis of anterior compression lesions in the frequent evident pyramidal tract signs. It may be that sectioning the dentate ligaments will avoid the often serious complications, if this is done before the cord is manipulated in any way.

In the laterally placed disks we have found that these can be removed through a hemilaminectomy or even a partial hemilaminectomy similar to the procedure used in the cervical region. If the nerve appears to be severely damaged a wider opening will be required in order to do a dorsal root rhizotomy. Epstein[1] also believes that dorsal rhizotomy is indicated for lateral disks to insure the relief of pain.

Much has been said against attempts at removal of bony spurs in this area, either central or lateral in location. We agree with Epstein[1] that these can usually be removed extradurally if the proper instruments are at hand.

SUMMARY

Ten patients with 12 thoracic intervertebral disk protrusions have been re-

ported and the location of another is included. A review of the literature up to December 1954 reveals a total of 51 thoracic disk protrusions. All of these except eight have been central or centrolateral disk protrusions. An additional six lateral disk protrusions are reported. Two patients each had multiple (two) disk protrusions.

The serious neurologic consequences of the central and centrolateral thoracic disk protrusions are confirmed in this series, again emphasizing the need for their early recognition and surgical treatment.

Particular attention is paid to the laterally placed disk protrusions in the thoracic region, since they give rise to symptoms similar to lateral disk protrusions in the cervical and lumbar areas (radicular pain and back pain). Many of these lesions go for months and years, erroneously thought to be visceral disease for which needless thoracic and abdominal operations are performed. Since surgical treatment leads to as favorable results as do the other lateral disk protrusions, early recognition and surgical attention is most desirable.

Myelography, if properly performed, will disclose defects caused by these lateral disk protrusions, and they are almost as reliable as in the cervical area.

Analysis of the cerebrospinal fluid has had no particular value in the diagnosis, though an increase in the total protein may indicate a large protrusion, usually central or centrolateral in position, resulting in some degree of obstruction at the site of the lesion.

Calcification of the intervertebral disk was not observed in this series, but has been reported by others.[2,3]

Contrary to the experience of others, trauma played an important etiologic role in four cases in this series and was a possible etiologic agent in another (case 5); hence it is probable that, if the proper congenital and degenerative conditions are present, trauma may be an etiologic factor in thoracic disk protrusions.

All thoracic disk protrusions can and should be diagnosed early and treated by surgical removal as soon as the diagnosis can be made. There is no place

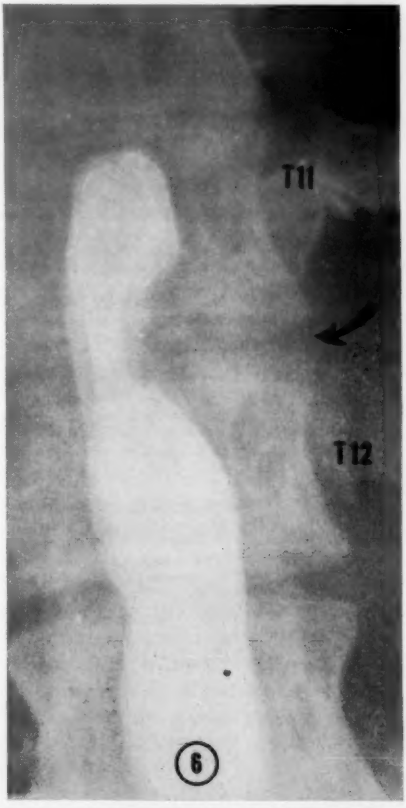

FIG. 6. Myelogram showing a defect opposite T11 on the right, consequent to a centrolateral disk protrusion. This same defect was found in all of nine films (see addendum).

for conservative or expectant management of any of these lesions. If treated properly, these lesions will benefit from surgery as favorably as disk protrusions in the cervical region.

ADDENDUM

Since this paper was submitted for publication we have treated another patient for thoracic disk protrusion (centrolateral T11, right).

A 29 year old laborer fell over backward from a height of 6 feet onto a bar on April 12, 1955. Immediately following the fall he experienced moderately severe back and leg pains which became so severe that two weeks after the accident opiates were required for relief. He was given various forms of physiotherapy without benefit.

At the time of the first examination on June 2, 1955, there were signs of early urinary retention and severe back muscle spasm. Lasegue's signs were strongly positive at 10 to 15 degrees bilaterally. There were no definite sensory or reflex changes noted. Percussion over the spinous processes of T10 and 11 elicited extreme radiating pain through the right eleventh dermatome and through the distribution of the cauda equina. The Pantopaque myelogram disclosed a fairly large centrolateral protrusion of the intervertebral disk at T11 on the right (figure 6). On June 9, 1955 this was confirmed by bilateral laminectomy at T11 and 12 and removal of the prolapsed disk.

The patient made a rapid recovery and left the hospital on June 18 with only minimal pain and without neurologic deficit. When last examined on August 8, 1955, he had mild lower back muscle spasm but was otherwise doing well. There was no neurologic defect.

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The Electroencephalogram in Head Injuries with Subdural Hematoma

Joseph G. Chusid, M.D. and C. G. de Gutierrez-Mahoney, M.D.

A REVIEW of our experiences in patients with verified subdural hematomas following head injuries was undertaken in an attempt to evaluate their electroencephalographic findings before and after operation, the possible factors contributing to electroencephalographic changes, and the place of electroencephalography among the procedures commonly used for the diagnosis of subdural hematoma.

MATERIAL AND METHODS

The electroencephalograms and clinical records of 55 patients with operatively confirmed subdural hematoma were reviewed. Electroencephalograms were made preoperatively in 34 patients and postoperatively in 38 patients; 17 of the preoperative group also had postoperative tracings.

The patients examined before operation were predominantly adults whose age range is indicated in table 1; 29 were male and five female. All cases were associated with a known head injury, and nine also had closed skull fractures. In seven instances the head injury occurred less than five days before the electroencephalogram, in nine cases the head injury occurred six to 15 days before the tracing, and in 18 cases the interval exceeded 15 days (table 2).

The postoperative group consisted mainly of adults whose age groups are indicated in table 1; 34 were male and four were female. Associated closed skull fracture was present in 12. Thirty patients whose initial postoperative record was made within a month after operative evacuation of subdural hematoma were designated as the early postoperative group (table 3). In this group the initial electroencephalogram was made in seven cases in the first postoperative week, in 15 cases in the second postoperative week, in six cases in the third postoperative week, and in two in the fourth postoperative week. Serial tracings were made in some cases. Patients comprising the late postoperative group were those in whom records were made more than three months after operation. This group, composed of 16 patients, included six patients of the early postoperative group and ten additional patients in whom the initial record was made three months or more after operation (table 4).

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Read by title at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 1955.

TABLE 1
AGE DISTRIBUTION BY DECADES

	1st	*2nd*	*3rd*	*4th*	*5th*	*6th*	*7th*	*8th*	*9th*
Preoperative (34 patients)	1	1	9	4	4	6	6	2	1
Postoperative (38 patients)	2	1	5	5	11	7	6	1	0

TABLE 2
INTERVAL BETWEEN INJURY AND INITIAL ELECTROENCEPHALOGRAM

	0–5 days	*6–15 days*	*16+ days*
Preoperative group	7	9	18

TABLE 3
INTERVAL BETWEEN OPERATION AND ELECTROENCEPHALOGRAM

	1 month						
	1 wk.	*2 wk.*	*3 wk.*	*4 wk.*	*3–6 months*	*6–12 months*	*12+ months*
Postoperative group	7	15	6	2	3	2	5

Electroencephalograms were made using ten or more scalp electrodes and two ear electrodes with conventional scalp-to-scalp and scalp-to-ear recording. The minimum recording time for each tracing was 20 minutes employing a Grass 8 channel electroencephalograph. Pneumoencephalograms were made in nine patients and carotid angiograms in seven before operation.

RESULTS

In the preoperative group of 34 patients, the electroencephalograms were classified as diffusely slow in 11 (32 per cent), slow focal in eight (21 per cent), slow focal with diminished amplitude in 14 (41 per cent), and normal in two (6 per cent) (table 4). In 19 (66 per cent) of 29 subjects with unilateral subdural hematoma, lateralization of the major abnormalities (slow focal, slow focal with diminished amplitude) coincided with the side of the hematoma. In two cases of chronic subdural hematoma, one ossifying in type, the record was normal. In eight unilateral cases the tracing was diffusely slow with no lateralization evident. Among the five patients with bilateral subdural hematomas, the major abnormality was on the side of the greater subdural collection in two cases, while diffuse slow nonlateralizing records were obtained in the remaining three. In none of this series was spike or sharp wave activity a prominent or significant feature.

In the early postoperative group of 30 patients, the electroencephalogram was classified as diffuse slow in ten (33 per cent), slow focal in nine (30 per cent), and slow focal with diminished amplitude in 11 (37 per cent). In the late postoperative group of 16 patients, the record was normal in seven (44 per cent), slow focal in three (19 per cent), spike focal in three (19 per cent), slow diffuse in two (12 per cent), and slow focal with diminished amplitude in one (6 per cent). In some patients where serial records were made, a return to normal was noted within a three to six month period (figure 1). Both patients of the preoperative group with normal records

TABLE 4
ELECTROENCEPHALOGRAMS — 55 PATIENTS WITH SUBDURAL HEMATOMA

	Diffuse Slow	*Focal Slow*	*Focal slow and diminished amplitude*	*Normal*	*Focal spike*
Preoperative (34 patients)					
Unilateral	8	6	13	2	0
Bilateral	3	1	1	0	0
Total	11 (32%)	7 (21%)	14 (41%)	2 (6%)	0
Postoperative (38 patients)					
Early (30 patients)					
Unilateral	6	7	11	0	0
Bilateral	4	2	0	0	0
Total	10 (33%)	9 (30%)	11 (37%)	0	0
Late (16 patients)	2 (12%)	3 (19%)	1 (6%)	7 (44%)	3 (19%)

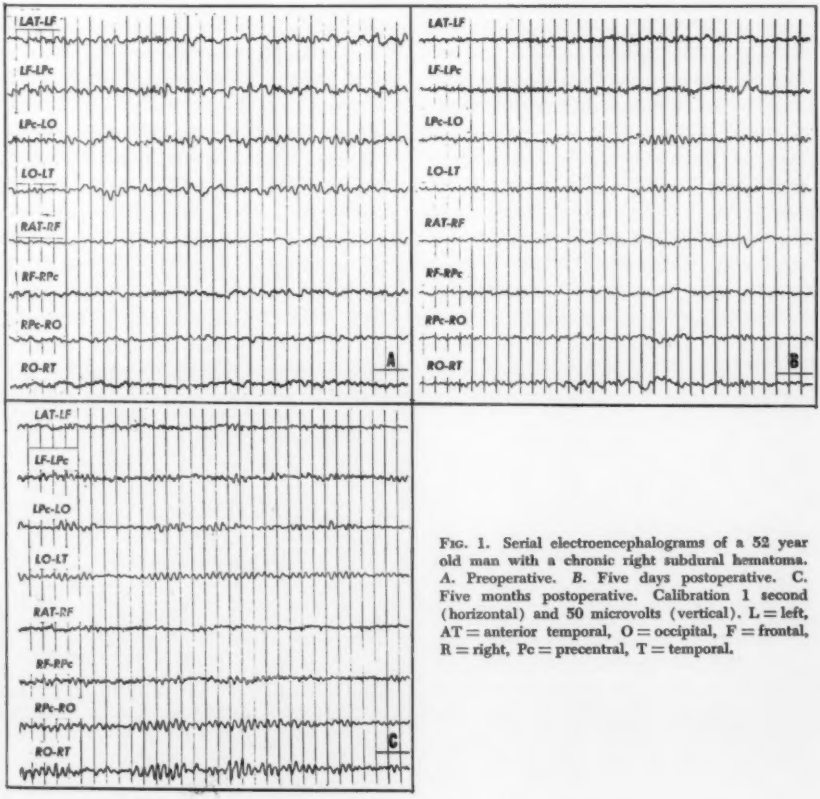

FIG. 1. Serial electroencephalograms of a 52 year old man with a chronic right subdural hematoma. *A*. Preoperative. *B*. Five days postoperative. C. Five months postoperative. Calibration 1 second (horizontal) and 50 microvolts (vertical). L = left, AT = anterior temporal, O = occipital, F = frontal, R = right, Pc = precentral, T = temporal.

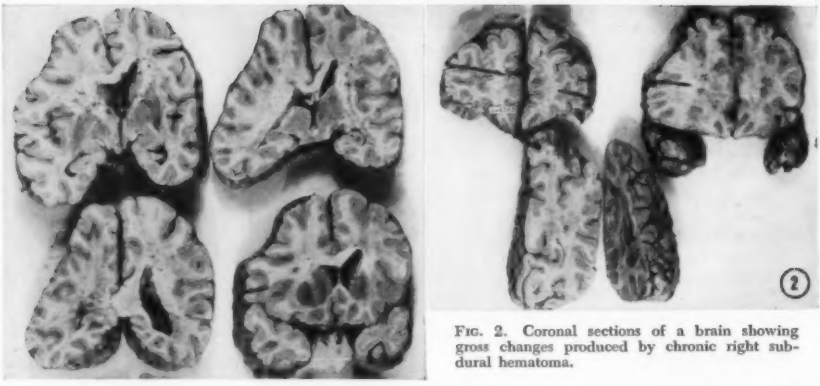

FIG. 2. Coronal sections of a brain showing gross changes produced by chronic right subdural hematoma.

were not included in the postoperative series since postoperative tracings were not obtained in these cases.

Pneumoencephalography revealed a shift to the opposite side and distortion of the lateral and third ventricles in eight of the nine patients on whom it was used; in the remaining case, the films were technically unsatisfactory. Percutaneous carotid angiography revealed the presence of subdural hematoma in six of seven patients on whom it was used; in the remaining case a satisfactory anteroposterior view was not obtained.

DISCUSSION

Our study indicates that when the electroencephalograms of patients with subdural hematomas are classified on the basis of the major abnormalities present, there is a similarity in the preoperative and early postoperative groups both in the types encountered and the relative incidence of these abnormal types. The evacuation of a subdural hematoma, while desirable or imperative from a clinical and therapeutic viewpoint, may not be associated with the immediate or prompt return of the tracing to normal within the early postoperative period (one month). These results also suggest that it might be difficult to distinguish head-injured patients with subdural hematoma from those without on the basis of the electroencephalogram alone.

Consideration of the associated pathologic brain changes likely to occur with subdural hematoma may indicate why removal of a subdural hematoma does not necessarily cause the electroencephalogram to return promptly to normal (figure 2). It must be remembered that the subdural hematoma itself is silent electrically, the potentials of the tracing being derived exclusively from brain tissue. Therefore, the electroencephalogram reflects the functional status of the brain itself. Pathophysiologic brain alterations occurring in the presence of a subdural hematoma may persist for prolonged periods of time after the evacuation of the subdural hematoma; continued distortion and shift of lateral and third ventricles may be demonstrated in pneumographic studies for some time after evacuation of a subdural hematoma (figure 3), so that the persistence of abnormal patterns through this period might be anticipated.

Studies of the pathologic changes associated with subdural hematoma have revealed that relatively widespread alterations may occur within the brain. Courville and Amyes[4] stated that increased intracranial pressure was the most common cause of death in fatal cases of dural hemorrhage. Vascular lesions, especially transient occlusion of the posterior cerebral arteries secondary to tentorial incisural herniation of a hippocampal gyrus as well as compression of the upper brainstem and hemorrhage into the basilar and tegmental portions, were also cited. The most common vascular complications encountered in a preliminary survey of their 300 autopsied cases of chronic subdural hematoma included hemorrhagic softening of the upper brainstem, softening of basilar surface of the temporo-occipital regions, softening of the anterior uncinate or hippocampal gyri, softening of the superior surface of the cerebellar hemispheres, softening of the cortex under the hematoma, patchy softening of the underlying white matter, and variable degrees of edema of the ipsilateral cerebral hemisphere. Compression of the lateral surface of the cerebrum by subdural hemorrhage according to Browder and Rabiner[1] may result in partial obliteration of the convexity of the underlying brain, displacement of the cerebral ventricular system of a variable degree, and swelling of the subcortical structures of the affected hemisphere involving the optic thalamus in particular, sometimes extending to implicate the brainstem.

In reviewing 310 verified cases of subdural hematoma, Munro[20] suggested that fatal issue was probably due to "medullary edema." Analysis by Craig and Miller[5] of the postmortem brain findings in 18 fatal cases of subdural hematoma showed cerebral edema (12 cases), cortical and subcortical hemorrhage (nine cases), infarction of cerebral hemisphere (eight cases), pontine hemorrhage (five cases), contusion of brain (four cases), degeneration of brain (three cases), laceration of brain (three cases), infarction of pons (three cases), and compression and distortion of brain (two cases).

Since many of the cases of our series were associated with severe head injury,

FIG. 3. Pneumoencephalograms of a patient with a chronic right subdural hematoma, before (right) and 12 days after (left) operation.

coexisting pathologic alterations of traumatic origin independent and unrelated to the subdural hematoma could also have occurred. In these circumstances the well established incidence in severe head injuries of laceration of the brain, diffuse contusions, especially in the subfrontal and temporal regions, massive intracerebral hemorrhages, petechial hemorrhages, as well as the action of coup-contracoup mechanisms could significantly modify brain structure and function. Cerebral swelling (tumefaction, edema, and liquefaction) was cited by Scheinker[22] as a common sequel of brain injury, the cerebral white matter being paritcularly vulnerable. He believed that petechial hemorrhages, massive intracerebral hemorrhages, disseminated foci of tissue destruction, massive hemorrhagic infarction of areas supplied by major blood vessels, and atrophic sclerosis of white matter might also occur after brain trauma.

Conflicting claims have been made regarding the electroencephalographic changes which may be expected in patients with subdural hematoma. Since the cerebral changes associated with head injuries may be similar in patients with or without subdural hematoma, and since the subdural hematoma itself is silent electrically, the tracings of these two groups may be difficult to distinguish from each other. According to Marsh and co-workers,[19] whose study of 13 cases indicated a variability in electroencephalographic tracings, this method could not be relied upon entirely in establishing a correct diagnosis. In six of nine unilateral cases, correct lateralization based upon ipsilateral dysrhythmia or "amplitude asymmetry" was possible. In two cases lateralization was wrong; in one case no lateralization was noted. In four bilateral subdural hematomas the larger lesion was diagnosed correctly in three cases by the occurrence of "suppression." Factors proposed by the authors which could account for misleading lateralizing and localizing phenomena included the transmission of abnormal potentials via commissural or association bundles, distortions and dislocations of the brain, and contrapressure. The findings in cases of adults with head injuries with and without unilateral subdural hematomas were identical and therefore impossible to differentiate according to Levy and co-workers.[15] Ipsilateral reduction in amplitude and slow wave foci were similarly present in the acute, subacute, or chronic stage in adults with or without subdural hematoma after head injury, so the initial tracing was of no value in differentiating the "operative" from the "nonoperative" type of head injury. Marinacci and associates[18] reported from a study of seven cases that, although the electroencephalogram might be of definite help in the diagnosis of cerebral lesions in infants and children, they did not consider the findings pathognomonic of subdural hematoma since the same electrical changes had been encountered with other intracranial lesions.

In the report of Cohn and associates,[3] five of six cases of subdural hematomas showed one of two primary characteristics: 1) a maximum of high voltage slow waves over the lesion (three cases) and 2) slow activity of reduced amplitude over the site of disturbance (two cases). The remaining patient had an essentially normal pattern despite the presence of a massive subdural collection of blood. Sjaardema and Glaser[23] stated that, in three verified cases of subdural hematoma, a pattern of high voltage beta and

delta waves was found which disappeared when the hemorrhge was removed. Although the pattern was not considered pathognomonic, it was believed to be of value as an adjunct in confirming the diagnosis of subdural hematoma.

In a review covering 25 consecutive cases of chronic subdural hematoma, Heersema and Freeman[10] stated that half of the cases disclosed unilateral delta waves which aided in localizing the lesion. In 38 per cent of the cases generalized or bilateral delta waves were found, while in the remaining 12 per cent the electroencephalograms were normal. Seven cases of surgically proved unilateral chronic subdural hematoma studied by Smith and co-workers[24] had preoperative electroencephalograms characterized by marked general asymmetry between hemispheres, with the hemisphere underlying the hematoma showing decreased amplitude and random low voltage slow waves. In the authors' opinion, variations in subdural hematoma cases could be explained by the presence of concomitant intracranial hemorrhage and/or brain damage. They stated that a period of five months might be required for the tracing to return to normal.

Friedländer[9] stated that the single most significant finding in 17 patients of his own and in 22 cases from the literature was focal slow activity which was present in 56 per cent of the cases. "Hypopotentia" in routine records was not considered by him to be a significant finding in patients with subdural hematomas. A study of 31 patients by Kaplan, Huber, and Browder[11] led them to state that the type of electrical activity found in the preoperative tracing had no bearing on the postoperative rapidity of improvement of the patient as determined by clinical or electroencephalographic studies. Their most frequent finding, present in 18 cases, was an "impeded effect" (lower amplitude, slower frequencies, and less sharply defined wave forms) on the side of the lesion.

In 20 of 24 patients with chronic subdural hematoma, correct presumptive diagnosis was made according to Lundervold and Nordlie[17] on the basis of ipsilateral decrease in amplitude with or without associated slow wave focus, or less frequently only a slow wave focus. The initial tracing in three cases was normal and in one case disclosed a slow wave focus on the opposite side.

The most significant finding in the series of surgically verified subdural hematomas reported by Rodin and coworkers[21] was the occurrence of focal slow waves. Of 37 adults and adolescents, focal or bilateral delta records with maximum incidence on one side were noted in 26 cases. Bilateral delta activity with no lateralization occurred in five cases, dysrhythmia without localizing features in four cases, and normal tracing in two cases. Postoperative recordings made in seven cases led them to state that after removal of the clot alpha rhythm returned to normal in about 14 days, while delta waves persisted for several weeks.

Abnormalities of two types were noted by Sullivan, Abbott, and Schwab[26] in 32 patients with subdural hematomas or hydromas: 1) suppression of alpha activity on the side of the lesion, which occurred in 13 of 24 unilateral hematomas and in two of the four unilateral hydromas, and 2) slow wave activity of either low or increased voltage, which occurred in 11 of the unilateral lesions and three of the four bilateral ones. The

electroencephalogram gave correct lateralization in 75 per cent of cases and correct localization on the side indicated in 47 per cent; it did not distinguish between unilateral and bilateral subdural accumulations, however. Davidoff and Feiring[6] noted that subdural hematomas, which sometimes occur as a delayed complication of the surgical treatment of congenital hydrocephalus, were correctly suspected in three cases because of the diminution in amplitude of electrical activity over an involved hemisphere.

Serial electroencephalography in acute head injuries was shown to be of considerable importance by Dawson and coworkers.[7] Very soon after injury the tracing may show little or no abnormality even though definite brain lesions are present. In the subacute and chronic phases of injury, however, they found that the electroencephalogram was a more valuable adjunct in diagnosis. Focal suppression, commonly encountered in acute head injuries, generally indicated the site of greatest injury in their opinion.

Very few studies have been undertaken upon experimentally induced subdural hematomas. Cohn[2] found that with acute subdural hematoma induced experimentally in cats there is decreased electrical activity over the side of "hemorrhage." In subdural hemorrhage of one week or more duration, 1) the focal decreased electric activity of the acute phase might persist in varying degrees; 2) there might be generalized slow waves with a maximum focal abnormality over the hemorrhage or adjacent area; or 3) an essentially normal pattern might be observed. In dogs with subdural or extradural lesions (injected wax), Ulett[27] noted ipsilateral disappearance of normal rapid activity and flattening in the acute phase.

OTHER DIAGNOSTIC STUDIES

Diagnostic studies other than electroencephalography commonly employed in the study of patients with suspected subdural hematoma include skull roentgenograms, pneumography, and cerebral angiography. Helpful information that may be derived from skull roentgenograms usually consists of evidence of pineal shift in the anteroposterior view, or rarely, shift of a calcified choroid plexus (figure 4) or calcification within the hematoma. Pneumography may aid by revealing distortion of the lateral and third ventricles with shift of these struc-

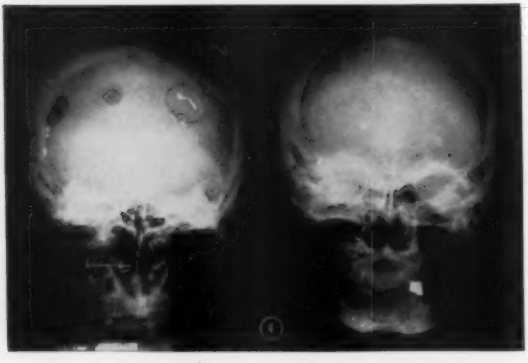

FIG. 4. Roentgenograms of the skull of a 62 year old man with a chronic left subdural hematoma showing medial and upward displacement of the calcified left choroid plexus in the preoperative film (right), with return to normal position in the postoperative film (left).

tures toward the opposite side. Limitations to the usefulness of these technics are imposed by the frequent absence of calcification of the pineal in the posteroanterior view and the failure of these tests adequately to distinguish shifts and distortions due to other reasons (tumors, edema, and so on).

In our experience, the most reliable diagnostic study short of operative exploration has been cerebral angiography, since a more or less specific pattern may be demonstrated in the majority of supratentorial extracerebral collections. The presence of normal cerebral angiographic patterns in the lateral and anteroposterior views in a head-injured patient suspected of supratentorial subdural hematoma may be considered to have practically ruled out this possibility. Carotid angiography, furthermore, is much less likely than pneumography to disturb seriously the dynamics of a compromised ventricular system and brain such as may be associated with subdural hematoma. In our patients percutaneous carotid angiography disclosed the subdural hematoma in six of the seven cases in which it was used. A characteristic pattern noted in the anteroposterior view during the arterial or capillary phase consisted of an avascular area subjacent to the cranial vault, usually with displacement of the anterior cerebral artery toward the opposite side (figure 5). In the case in which angiography failed, the critical anteroposterior view was unsatisfactory.

Carotid angiography has been successfully used by others for the diagnosis of subdural hematoma. Percutaneous cerebral angiography was first advocated as a valuable diagnostic aid in patients with head injuries by Löhr,[13,14] who described the characteristic depression of the superficial cerebral arteries from the inner table of the skull with extradural and subdural hematomas. Zehnder's[30] review of subdural hematoma included the reproduction of a striking Thorotrast carotid angiogram of a 14 year old youth with a subdural hematoma. Cerebral angiography permitted differential diagnosis between extracerebral and intracerebral hemorrhage, according to Kristiansen[12] and Wickbom,[29] who claimed it was superior to exploratory operation in this respect. Lima[16] stated that the angiographic diagnosis of subdural hematoma depends principally upon the appearance of avascular zones of lenticular shape, sometimes associated with secondary vascular displacements. Engeset[8] reported that the angiograms of 14 of 21 patients with subdural hematoma revealed a characteristic avascular

FIG. 5. Anteroposterior view of a carotid angiogram demonstrating the chronic right subdural hematoma of the patient whose electroencephalographic tracings appear in figure 1.

area between the skull and the compressed part of the brain.

Webster and associates[28] made angiographic studies on 30 seriously ill patients with head injury suspected of massive intracranial hemorrhage. Typical vascular patterns were found to distinguish the subdural, epidural, and intracerebral hematomas, and in their series all nine subdural hematomas were correctly diagnosed. The authors stated that they considered angiography superior to the more complicated and possibly inaccurate exploratory trephine. Stein[25] reported that, in six of seven patients with verified unilateral subdural hematoma among a group of 15 suspected of subdural hematoma, percutaneous cerebral angiography correctly demonstrated the hematoma.

SUMMARY

1. Electroencephalographic studies were made on 55 patients with head injuries and verified subdural hematomas, 34 of whom were studied before and 38 after operation.

2. Classification of the electroencephalograms according to major abnormalities revealed that abnormal types and their incidence were similar in the preoperative and early postoperative groups. Tracings were usually found to be of the following types: diffuse slow, focal slow, or focal slow with diminished amplitude. In 19 (66 per cent) of 29 unilateral subdural hematomas in the preoperative group, lateralization of major abnormalities (slow focal, slow focal with diminished amplitude) coincided with the side of the hematoma.

3. Brain changes which may be associated with head injuries and subdural hematomas were reviewed. Cerebral contusion, laceration, hemorrhage, infarct, compression, swelling, distortion, increased intracranial pressure, and coup-contrecoup mechanisms may affect the electroencephalogram independently of a subdural hematoma.

4. Studies cited from the literature dealing with preoperative tracings in patients with subdural hematoma revealed considerable disagreement in the reported findings and their significance.

5. Cerebral angiography is a more reliable and accurate test for the demonstration of supratentorial subdural hematoma in adults with head injuries than other commonly employed diagnostic tests (skull roentgenograms, electroencephalography, pneumography).

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■ There are some animals in which the decussation in the spinal cord is not so complete and so immediate as it is in mammals; such are reptiles and birds. This is one of the causes of some mistakes recently made by an able experimenter, Mr. Chauveau, of Lyons. He operated upon pigeons, and found that after a section of a lateral half of the spinal cord, sensibility seemed to be much diminished on the same side, and not at all on the opposite side. He concluded, therefore, that there is no decussation. I have ascertained that the results of the experiments vary with the place of the section. If it be made just above the lumbar enlargement, where Mr. Chauveau makes it, the decussation having hardly begun below this place, the results are as he says; but if the section be made two inches higher, in the dorsal region, there is, as in mammals, though less marked, an increased sensibility in the posterior limb on the side of the section, and a diminution of sensibility in the opposite limb. The loss of sensibility is never complete, showing that the decussation is not complete. The same results are obtained in reptiles.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Arnold-Chiari Malformation with Associated Analogous Malformation of the Midbrain

Irwin Feigin, M.D.

THE ARNOLD-CHIARI MALFORMATION [1-4] is a relatively uncommon abnormality in which there is a caudal displacement of portions of the cerebellum and medulla into the spinal canal, often with an overfolding or partial reduplication of medullary tissues at the junction with the spinal cord and with an upward angulation of the upper cervical nerve roots. In the rare instances in which the cerebellar deformity or the medullary deformity is found without the other, the former has been designated as the Arnold malformation, the latter as the Chiari malformation. The Arnold-Chiari malformation is found most commonly in children, and is usually associated with a meningomyelocele or meningocele and with hydrocephalus. It is sometimes found in adults, and its recognition has gained greater significance since the development of surgical technics to alleviate the clinical disorders associated with it. A controversy exists as to its pathogenesis, some favoring the concept that it is caused mechanically by traction from below or pressure from above, while others implicate a developmental anomaly. This paper will describe three cases of cerebral malformation in infants, in which the presence of other malformations, particularly an analogous malformation of the midbrain, would favor the concept of the developmental character of this entity.

Case 1.—An infant was stillborn at term. The mother was primipara, Rh positive, and had had no difficulties during pregnancy. The fetal heart had been noted to be slow and irregular about ten minutes prior to birth. The head was enlarged and a podalic extraction and craniotomy was performed to facilitate delivery.

Autopsy showed an enlarged skull measuring 38 cm. in circumference, with a wide separation of the sutures and a fracture of the left parietal bone. There was a roughly ovoid defect in the skin overlying the spine from the eleventh dorsal to the first sacral segment, measuring approximately 4.5 cm. in length and 3.5 cm. in width. This defect was covered by a thin, translucent gray membrane. There was a wide gaping defect of the dorsal laminae of the vertebrae in the region cited measuring 7 cm. long and 3 cm. wide. An intact spinal cord segment was present in the cephalic portion of the defect, but the cord was flattened and indistinguishable from the connective tissues at the base of the defect in its more caudal portion. The fibers of the cauda equina could be seen matted together in this area.

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FIG. 1. *Case 1.* Midbrain and cerebellum, dorsal view. The caudal portion of the cerebellum is congested and shows obscured folial outlines. The dorsal vermis is not well defined. The inferior colliculi form a conical mass projecting backward over the cerebellum and pons.

FIG. 2. Midbrain and cerebellum, lateral view. The caudal projection of the midbrain is seen to better advantage.

The brain was enlarged, measuring 15x10x7 cm. in size. The cerebral hemispheres were approximately symmetric. The gyral pattern was of increased complexity, the gyri being somewhat increased in number, decreased in size, and arranged in an irregular fashion. The cerebellum was subdivided into two portions, an anterior segment of normal cerebellar tissue 5 cm. wide and 3 cm. long, and a caudal segment of purple, markedly congested tissues with obscured folial outlines 32 mm. in width and 11 mm. in length (figure 1). A dorsal vermis was not recognized. The tissues of the corpora quadrigemina formed a prominent projection backward, overlying the anterior medullary velum and forming a conical mass approximately 7 mm. in diameter and 2 to 3 mm. in length (figure 2). The pons appeared normal. The medulla was covered dorsally by a thin layer of purple fleshy tissue 2 mm. in thickness, 9 mm. in length, and 12 mm. in width. The medulla was elongated, extending to the region of the seventh cervical vertebra. At this point a deep semicircular indentation delimited the medulla from the cord which lay anteriorly. The cephalic portion of the cord was 12 mm. wide at this point, but narrowed down caudally in a funnel-shaped fashion to approximately 8 mm. in width. The nerve roots were directed upward and laterally in the cephalic region. The remaining cord was normal except in the region of the spina bifida, where it became flattened and enmeshed in the connective tissues at the base of the ulcerated defect.

Section of the cerebrum revealed the cerebral tissues to be compressed as a result of an internal hydrocephalus, the cortex and white matter averaging about 1 cm. in thickness. The parenchymal vessels were congested and scattered areas of petechial hemorrhage were present. These were not concentrated in the right parietal area, and there was no other change which could be correlated with the fracture of the right parietal bone. As is usual, the compression of the white matter was far greater than the compression of the cortex or the gray matter of the basal structures. The fornices and the septum pellucidum were completely absent, and the corpus callosum was represented by a very thin layer of neural tissue less than 1 mm. in thickness which served as the dorsal limit of the conjoined ventricular system. A similar membrane, perhaps even more delicate, formed the ventral boundary of the ventricular system of the cerebrum. The dilatation of the lateral ventricles was least marked frontally and most marked occipitally. The ependymal surface of the greatly dilated occipital horns presented a large number of small, moist, firm, rounded elevations varying from 3 to 8 mm. in size. Anteriorly the third ventricle was very small, measuring 4 mm. dorsoventrally and 5 mm. laterally, and was traversed laterally in a horizontal plane by a band of tissue 2 mm. in diameter which may have represented the massa intermedia. No communication was recognized between this cavity and the lateral ventricles. Posteriorly the third ventricle widened some-

what, measuring 11 mm. laterally and 6 mm. dorsoventrally, and extended to and communicated with the aqueduct. The cephalic portion of the aqueduct formed a vertical slit 3 mm. in height and less than 1 mm. in width. Caudally the lumen was recognized only as a barely perceptible area of gray coloration 2 mm. in height and of barely perceptible width. More caudally the presence of blood revealed the site of the aqueduct which nowhere measured more than 1 mm. in greatest diameter. It communicated with the fourth ventricle, which consisted of a slit-like cavity approximately 1 mm. in height and 9 mm. in width. Posteriorly the ventricle continued as a broad funnel-shaped passage ventrally into the substance of the lower medulla to form the central canal. At a point just below this level the medulla appeared to be reduplicated, there being a ventral mass of compressed congested purple tissue lying beneath a dorsal medullary segment. The cervical cord in this area showed irregular purple areas of discoloration and a rare petechial hemorrhage. More distally the cervical cord contained a cavity 3x1 mm. in size which lay transversely in the dorsal tissues of the cord.

Microscopic section of the cerebral cortex did not disclose any marked abnormality in cytoarchitecture. The vessels of the cortex and subcortical white matter were congested, and there was some extravasation into the perivascular spaces. The ependyma of the lateral ventricles appeared normal, and the usual variety of primitive cells was present in the subependymal area. The subependymal nodules consisted grossly of collections of neurons arranged without order. In most nodules the neurons were of approximately the same order of maturity as those in the cortex, but in some, primitive cells were present in moderate numbers and one consisted entirely of primitive cells. The thin septae forming the dorsal and ventral boundaries of the lateral ventricles consisted of thin layers of glial tissue, covered on one aspect by leptomeninges and on the other by an incomplete layer of ependymal cells. The tissues of the anterior portion of the third ventricle contained numerous small, irregular ependymal-lined channels. The midbrain was of an unusual triangular shape. The caudal portion of the aqueduct was markedly decreased in size, but was not completely occluded. Hemorrhage was present within it. There was no gliosis or islands of buried ependymal cells to indicate that this stenosis was acquired. The tissues dorsal to the aqueduct were of increased thickness and consisted of neurons and glial cells in normal proportions arranged irregularly. An invagination of leptomeninges in these tissues was represented on section by a midline cavity within the tectum. On both sides of this cavity a series of small ependymal-lined channels extended dorsally to reach a point about half way to the dorsal surface of the tectum. The meninges contained a large number of heterotopic glial nests. The pons revealed a few petechial hemorrhages, congested vessels, and an occasional heterotopic glial nest. Most of the cerebellar tissues were normal except for congestion, petechial hemorrhages, and slight hemorrhage into the leptomeninges. That portion of the caudal cerebellum which appeared purple and soft on gross inspection contained areas of profound neuron loss in the cortex, with a marked proliferation of astrocytes and astrocytic fibers. Some of the affected folia contained cystic cavities replacing much of the white matter and lined by condensed glial tissues. Rarely a few fine collagen fibers were noted as well, apparently extending from the walls of adjacent vessels. The leptomeninges of the medulla were markedly thickened and fibrotic, and in one area contained a great many dilated vessels which assumed the form of an angioma. Such angiomatous tissue constituted the purplish tissue seen grossly on the ventral aspect of the medulla. Large numbers of dilated, congested vessels were also present with the parenchyma, resembling an angioma in appearance. Focal areas of hemorrhage were also present. The cervical spinal cord contained a cystic cavity dorsal to the central canal and lined with condensed glial tissues. The tissues beneath the spinal defect included an irregular admixture of connective tissues, with tissues containing ependymal cells, neurons, glia, and peripheral nerve tissue.

Summary. Autopsy of a stillborn infant revealed a meningomyelocele associated with a series of malformations which included an agenesis of the septum pellucidum and fornices, the formation of an abortive corpus callosum, a malformed third ventricle, a partial stenosis of the aqueduct, hydrocephalus, heterotopic masses of gray matter beneath the ependyma of the lateral ventricles, syringomyelia, similar cysts in the cerebellum, the absence of a dorsal vermis, angiomata, a suggestive microgyria, an

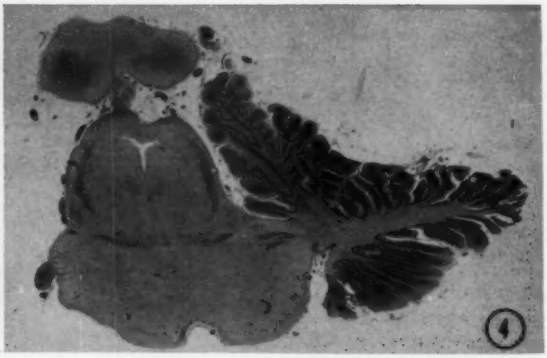

FIG. 3. *Case 2.* Midbrain and pons, lateral view. The inferior colliculi project backward in a conical mass overlying the pons.

FIG. 4. Cross section at junction of midbrain, pons, and cerebellum. The caudal projection of the midbrain overlies the anterior velum and is connected to it by a thin glial septum. Phosphotungstic acid hematoxylin stain.

Arnold-Chiari malformation, and an analogous malformation of the midbrain.

Case 2.—A male infant was delivered at term by forceps after a difficult prolonged labor. At birth a well-demarcated lesion 12 cm. in diameter was noted in the lumbosacral area. It was covered by a thin translucent membrane, the central portion of which was roughened and hemorrhagic. The lower extremities were flaccid and apparently anesthetic, and there was no tone in the anal sphincter. The infant was given prophylactic antibiotics as a temporizing measure until surgery became possible. However, an acute respiratory infection supervened and the infant expired 27 days after birth. There was no evidence of an increase in the size of the skull.

Autopsy revealed acute inflammation of the trachea and bronchi, with evidence of aspiration and with focal areas of pulmonary atelectasis. The left adrenal vein was thrombosed, and hemorrhage was present in the adrenal gland. A left hydrocele was noted. The spinal column revealed a dorsal kyphosis. The skull was deformed, the posterior fossa being rounded and funnel-shaped toward the foramen magnum. The bony ridges at the base were more prominent than normal, particularly with respect to the labyrinthine canals, the transverse supraorbital ridges, and the ridges of the middle fossa.

The brain was approximately normal in size. The cerebral gyral pattern was very complex, the gyri being increased in number and decreased in width. The sulci were normal. The cerebellum appeared small and was somewhat conical in shape, as would be required by its position in the funnel-shaped posterior fossa. At the time of removal, no evidence of herniation of cerebellar tissues or caudal displacement of the medulla was noted. These tissues were macerated during removal. Examination later revealed no external changes in the medulla. The pons appeared small. The caudal portion of the corpora quadrigemina projected caudad for a distance of approximately 4 mm. overlying the pons, with a small tab of cerebellar tissue interposed (figure 3). This projection was approximately 10 mm. in height and width at its base and tapered conically to reach a diameter of about 3 mm. at its distal tip. On section of the cerebrum, the lateral ventricles were noted to be slightly dilated, as was the third ventricle. The aqueduct appeared to be compressed laterally throughout most of its course. The fourth ventricle showed no changes. The spinal cord was normal except in the region of a spinal defect, where it became flattened and fused with the connective tissues forming the base of the defect. Numerous nerve roots could be traced to the inferior surface of the skin.

Microscopic sections revealed a small number of red cells in the subarachnoid space associated with a slight proliferation of arachnoid cells.

The neurons of the cortex were decreased in number, and the linear character of their arrangement was partially obscured. The neurons were of moderate size, but the orientation of their apical dendrites was clearly irregular. The white matter appeared normal. The subependymal tissues contained many primitive cells. The basal ganglia showed no changes. The midbrain meninges revealed many heterotopic glial nests. The aqueduct was compressed laterally. The caudal protrusion of the dorsal midbrain was seen to consist of a moderate number of apparently normal, small and medium-sized neurons diffusely distributed, together with a moderate number of glial cells in approximately normal proportions. A few myelinated fibers were present. Two small rosette-like nests of ependymal cells were present approximately in the midline. This tissue mass was connected on one side to the anterior medullary velum by a thin septum of glial tissue (figure 4). This showed increased cellularity, with a greater proportion of glial fibers and a small ependymal-lined channel. These tissues also contained a small space containing leptomeninges, apparently an invagination from the surface. The pons, medulla, and cerebellum were intrinsically normal, although the leptomeninges between some of the cerebellar folia were incompletely split.

Summary. A 27 day old male infant with a lumbosacral meningomyelocele died of an acute respiratory infection. Gross evidence of an Arnold-Chiari malformation was not noted at the time of removal of the brain, and these tissues were macerated during removal. Microscopic examination of the brain revealed microgyria, a mild hydrocephalus, and a malformation of the caudal portion of the tectum of the midbrain.

Case 3.—An infant was born at term after a short, uncomplicated, spontaneous delivery. The mother was normal and the pregnancy was uneventful. The mother and baby were both Rh negative. A defect measuring 4x4 cm. was present in the dorsal laminae of the upper lumbar spine and covered by a thin, translucent membrane. The roots of the cauda equina and the spinal cord were visible through the membrane on transillumination. The lower extremities were completely flaccid, and no deep reflexes were present. The lower extremities were thought to be anesthetic. The anal sphincter was hypotonic. There was an almost constant dribbling of urine. The infant was treated conservatively until it became apparent that a hydrocephalus was developing. Phenolsulfonphthalein studies revealed less than 5 per cent of the dye in the urine after 1 cc. had been injected into the lateral ventricles. A tilt test, however, suggested that a communication existed between the ventricles and the lumbar sac. A unilateral choroid plexectomy was performed about five weeks after birth. The postoperative course was good for three days, following which an *E. coli* infection of the subarachnoid space became apparent, and death supervened one month postoperatively in spite of vigorous therapy.

Autopsy showed the lungs to be atelectatic. The skull showed areas of lacunar thinning. The brain was enlarged, and there was obvious collapse of enlarged hydrocephalic cavities. The cerebral gyral pattern appeared unusually complex and some gyri were unusually narrow. An operative defect was noted in the right occipital area of the brain, to which a portion of the dura and calvarium were firmly adherent. A thick plastic exudate was present on the external aspect of these connective tissues. The lateral ventricles were markedly and symmetrically dilated, and the ependymal surfaces were covered by a relatively smooth, thick, plastic exudate. The caudal portion of the medulla presented a bulbous deformity projecting caudad dorsal to the proximal cord (figures 5 and 6). This bulbous deformity measured 9 mm. in length, 5 mm. in height, and 10 mm. in width. The entire medulla was elongated, measuring 57 mm. in length. A mass of cerebellar tissue was present in the midline dorsally, which appeared to represent a deformed dorsal vermis. A minimal herniation of the caudal cerebellar tissue approximately 3 mm. in length was noted ventrally (figure 5). The caudal midbrain dorsally presented a caudal projection of tissue analogous to that in the medulla, which measured 7 mm. in length (figure 5 and 6). It was 13 mm. in width at its base, but narrowed rapidly to a width of 1 to 2 mm. at its pointed caudal extremity. Its height varied similarly from 8 mm. at the base to 1 or 2 mm. at its caudal extremity. This mass projected backward to lie over the anterior aspect of the cerebellum and pons. The cerebral peduncles were flattened, the midbrain assuming a triangular shape on cross section. The aqueduct was small but patent throughout. The fourth ventricle was

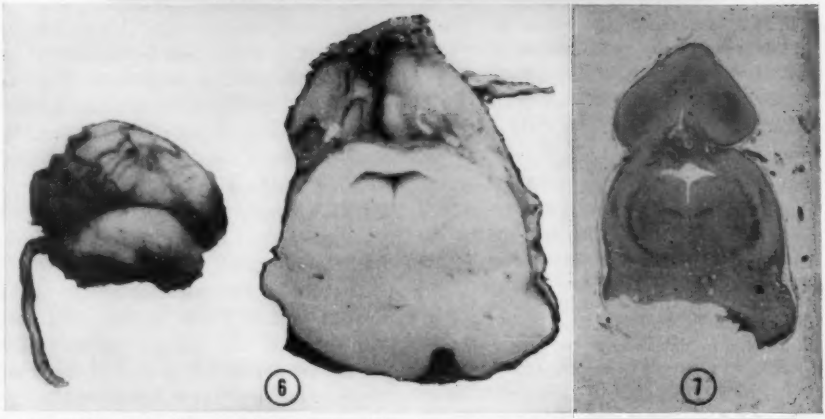

FIG. 5. *Case 3.* Midbrain, cerebellum, and medulla, dorsal view. There is a caudal projection of the inferior colliculi backward over the cerebellum. The dorsal vermis is poorly formed. A thin segment of herniated cerebellar tissue is present caudally. The medulla is elongated and reveals a bulbous dorsal projection overlying the spinal cord.
FIG. 6. Junction of medulla and cord (left), junction of midbrain and pons (right), posterior view. The caudal projection of midbrain over pons resembles that of medulla over cord.
FIG. 7. Cross section at junction of midbrain and pons. There is a conical projection of midbrain tissues overlying the anterior velum. Phosphotungstic acid hematoxylin stain.

small and flattened superoinferiorly. The pons and medulla were also somewhat flattened superoinferiorly. The proximal portion of the central canal of the spinal cord was fairly wide and patent. The spinal cord revealed leptomeningeal opacity throughout, but otherwise appeared normal except in the region of the meningocele where the nerve roots became adherent to the connective tissues covering the bony defect. A plastic exudate was noted covering these connective tissues.

Microscopic examination revealed a moderate infiltration of the cerebral leptomeninges by lymphocytes and polymorphonuclear leukocytes, with a moderate to marked proliferation of arachnoid cells. The spinal leptomeninges were much more severely involved, being thickened, fibrotic, and infiltrated by larger numbers of

lymphocytes, a few plasma cells, and a few polymorphonuclear leukocytes, and showing a moderate to marked proliferation of arachnoid cells. The dural connective tissues covering the operative defect occipitally and the connective tissues of the meningocele sac were each covered by a thick fibrinopurulent exudate and revealed evidence of the formation of a more chronic inflammatory granulation tissue as well. The ependymal surfaces of the lateral, third, and fourth ventricles were covered by a thick fibrinopurulent exudate. The remnants of the choroid plexus of the right lateral ventricle were completely necrotic, and this and the other choroid plexuses were infiltrated and covered by an acute inflammatory exudate.

The cerebral cortex was essentially normal. The white matter was thinned and showed considerable rarefaction and edema, with a proliferation of microglia, astrocytes, and astrocytic fibers in the subependymal zones. The vessels in this area were congested and some were occluded by fresh fibrin thrombi. Many showed an infiltration of their wall by lymphocytes and many large mononuclear cells were present in the perivascular spaces. Similar changes were present in the subependymal tissues of the aqueduct and fourth ventricle. Here many of the vessels also showed deposition of a finely fibrillar, slightly basophyllic material in the perivascular spaces. This material was slightly metachromatic with toluidine blue in an aqueous medium. The caudal projection of the dorsal midbrain contained many small neurons distributed irregularly and glial cells in approximately normal proportion and appearance. It contained an irregular cavity with leptomeningeal tissues showing inflammatory changes, apparently an invagination of the subarachnoid space (figure 7). The tissues of the caudal projection of the medulla showed no histologic deviation, except for marked inflammation as described above. The choroid plexus of the fourth ventricle was considerably hypertrophied and hyperplastic and extended dorsally through atrophic cerebellar tissues to reach the leptomeninges. The cerebellar tissues were histologically normal. The spinal cord tissues were intrinsically normal except for inflammatory vascular changes and contained a widely patent central canal. The meningocele tissues were infiltrated by a partially necrotic fibrinopurulent exudate. Numerous peripheral nerves were recognized, but no central nervous tissue was identified.

Summary. A newborn infant with a spinal meningocele developed hydrocephalus and was subjected to a choroid plexectomy. A leptomeningeal and ependymal infection supervened and the infant expired at nine weeks of age. At autopsy, in addition to the infection, a series of congenital malformations were observed, which included a spinal meningocele, a suggestive microgyria, an internal hydrocephalus, a malformation of the choroid plexus of the fourth ventricle, an Arnold-Chiari malformation, and an analogous malformation of the midbrain.

DISCUSSION

The Arnold-Chiari malformation occurs most frequently in infants and is usually associated with spina bifida and associated anomalies. Russell states that careful study will disclose this malformation in all cases of meningomyelocele, in contradistinction to only some cases of meningocele.[5] She considers the malformation to be a developmental anomaly, often associated with other malformations in addition to the spinal changes. An alternative interpretation for such cases, as offered by Lichtenstein,[6] would implicate the fixation of the lower spinal cord at the meningomyelocele site as the primary difficulty. It is suggested that with growth the normal upward displacement of the lower end of the cord is prevented, so that traction on the upper segments pulls the hindbrain downward into the foramen magnum. As pointed out by others, it is difficult to see how traction from below could cause the nodular angulation of the medulla seen in many of these cases, nor why the deformity should occur in high thoracic meningomyeloceles[5,7] and not in some cases of sacral meningocele where fixation at that level was demonstrated.[5,8] It has also been suggested that this deformity is secondary to the associated hydrocephalus, the pressure from above

pushing the hindbrain into the cervical canal. However, there are cases in which this deformity is recognized in the absence of hydrocephalus or of significantly increased intracranial pressure.[5,9]

There are cases to which the term Arnold-Chiari malformation has been applied in which a protrusion of cerebellar tissues into the foramen magnum clearly results from increased intracranial pressure, particularly in the posterior fossa.[10,11] Gardner and Goodall[11] referred to an "acquired Arnold-Chiari malformation" due to an acoustic nerve tumor. As far as is known, medullary herniation is not described in such circumstances, nor has the medullary nodular angulation been noted.

Deformities of the bones of the skull, particularly platybasia, may obviously be associated with deformities of the cranial contents, and these may result in changes very much like those under discussion.[12] In many of these cases the functional and physiologic alterations are of great importance, warranting careful clinical study to permit surgical alleviation.[13] From a pathogenetic point of view, however, the consideration of these cases with those without such obvious cause should be held in abeyance.

There remains a group of cases, generally older children or adults, in which this deformity is recognized in the absence of significant spinal or cranial defects or intracranial expanding lesions. The pathogenesis of these cases can be inferred only from a study of the entire group. The effect of traction from below can be excluded in those cases in which spinal anomalies were not present,[14–17] and reasons for excluding this factor in cases with spina bifida have already been stated. Pressure from above can be excluded in those cases without hydrocephalus [15,17,18,59] and, as will be discussed below, hydrocephalus may result from this malformation rather than cause it.

In a positive sense the presence of other malformations tends to support the contention that this lesion is also a developmental anomaly. A frequent concomitant anomaly is the absence of the cerebellar vermis, a change which could not possibly be mechanical.[9,15,17,19] The spina bifida and associated changes may be coincidental anomalies, not causally related. It is quite possible that the Arnold-Chiari malformation accompanying skull changes such as platybasia is an associated developmental anomaly, at least in part, and not entirely secondary to mechanical factors. In the case reported by Chorobski and Stepien,[19] the Arnold-Chiari malformation occurred together with platybasia and an absent vermis, suggesting that both osseous and neural changes were primary malformations. Our present embryologic theories on the mutual interdependence of adjacent or related structures on the development of each would lead to such expectation.

Hydrocephalus is a frequent but not constant concomitant. Russell[5,9] has suggested that the caudal displacement of the foramina of Lushka and Magendie into the spinal canal, while permitting free flow to the lumbar sac, results in a partial or complete blockage of flow back into the cerebral subarachnoid space when the foramen magnum is blocked by the herniated tissues. Since a major portion of the cerebrospinal fluid is reabsorbed from the cerebral subarachnoid space, the loss of this reabsorptive capacity may result in hydrocephalus. This would explain the occurrence of severe bacterial inflammation of

the spinal leptomeninges and ventricular ependyma with relative sparing of the cerebral leptomeninges, as in cases cited by Russell[5,9] and in case 3 of this report. The phenolsulfonphthalein studies were also consistent with this theory, showing a free communication between the ventricles and the lumbar sac, while the deficient urinary excretion may have reflected decreased reabsorption due to blockage between these structures and the cerebral subarachnoid space. The aqueductal narrowing implicated by Lichtenstein[6] as part of the traction mechanism is not observed in all cases.

Abnormalities in the midbrain have been described by Russell and Donald[9] and by Ogryzlo.[15] They described some cases in which the colliculi were poorly formed and fused into a rounded or conical elevation or a compressed median ridge. In the three cases presented in this paper, the colliculi formed a conical projection backward overlying the pons and cerebellum, so that a structure was formed very much like the similar dorsal projections of the medulla in the Arnold-Chiari malformations (figures 2, 3, 4, 6, and 7). These projections ranged from 5 to 8 mm. in height and extended caudally over the anterior velum for 2 to 7 mm. The distal extremity tended to be pointed. Microscopically, the tissues consisted of small neurons distributed irregularly and glial cells in approximately normal proportions. Heterotopic glial nests were present in the subarachnoid space of the malformed tissue in two instances and in adjacent tissues in the third. In each case the projecting tissues encompassed an invagination of the subarachnoid space, which appeared circular on cross section. In two instances the malformed tissues contained a number of irregular ependymal-lined channels, some of which were partially obliterated. In one instance there was a narrow septum of glial tissue like an elongated frenulum connecting the malformed tissues to the anterior medullary velum (figure 4).

Other cerebral malformations were present in each case, in addition to the spina bifida, the meningomyelocele, and the midbrain malformation just described. Two cases presented the classical Arnold-Chiari malformation (figures 1 and 5), and these were associated with a marked hydrocephalus. In the second case no medullary or cerebellar malformation was observed at the time the brain was removed at autopsy, and these tissues were partly macerated in removal precluding more careful observations after fixation. A meningomyelocele was present, so that an Arnold-Chiari malformation may have been anticipated, as suggested by Russell's observations on the constancy of such association.[5] The posterior fossa of the skull was deformed, being rounded and funnel-shaped toward the foramen magnum. There was little hydrocephalus in this case. This excludes the possibility that the midbrain malformation in this case was the result of mechanical pressure from above against the crura of the tentorium. In any case, such a mechanical factor would have obliterated the thin glial septum present in this case (figure 4) which extended from the midbrain malformation to the anterior velum. Microgyria was present in one case and suggestively present in the others. A malformation of the choroid plexus was noted in one case; an agenesis of the septum pellucidum and fornices, a malformation of the third ventricle, a partial stenosis of the aqueduct, numerous subependymal nodules of heterotopic gray matter, ab-

sence of dorsal vermis, and glial-lined cavities in the cerebellar cortex and spinal cord were present in another. The coexistence of these malformations would also suggest that the midbrain malformation and the Arnold-Chiari malformation were developmental rather than mechanical in origin. On the other hand, the cavities in the cerebellar tissues are most probably secondary to compression and interference with circulation, supporting Lichtenstein's contention[20] of a similar pathogenesis for the syringomyelic cavities in the cord.

It is of interest that illustrations of the brain of the human fetus of approximately 14 to 50 mm. in length[21] show a similar caudal projection of the corpora quadrigemina. This suggests that it may be the result of developmental arrest.

SUMMARY

Autopsies of three infants showed a pyramidal deformity of the caudal portion of the tectum of the midbrain which projected backward over the cerebellum and pons in a manner resembling the dorsal projections of medullary tissue over spinal cord commonly seen in the Arnold-Chiari malformation. All revealed lumbar spinal defects with meningomyelocele, and two revealed the classical Arnold-Chiari malformation. These and other varied developmental deformities support the contention that they were not due solely to mechanical factors. The occurrence of a stage in normal embryonal development in which the tectum of the midbrain assumes the form shown in these deformities suggests the possibility of developmental arrest.

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Is Pain Due to Pressure on Nerves?

Spinal Tumors and the Intervertebral Disk

Michael Kelly, M.D.

THE PRESSURE THEORY of pain has come to occupy its present position largely by default. It has never been challenged, though it never has been proved. It has come to be accepted as self-evident that the common stimulus for pain is pressure or tension on nerve fibrils and free endings. When the cause of a pain is unknown, we only have to suggest some mechanism which will generate pressure or tension and it stands explained.

Thus, sciatica is attributed to pressure on lumbar roots and arm pain to pressure on roots or plexus. Posttraumatic headache is said to come from tension on meningeal adhesions and migraine from stretching of pain fibrils in the dilated temporal arteries. Pain from a scar is attributed to tension on an adherent nerve trunk and lightning pains of tabes to fibrosis with compression of posterior columns. The pain which accompanies inflammation is due to the pressure which is generated in the tissues. Colicky pain is caused by pressure on visceral nerve endings by contracting smooth muscle.[1]

These examples could be multiplied many times. From case to case there are wide differences in the amount of pressure and in the mechanism by which it is applied. In most cases fine nerve fibrils are said to be compressed, in others large trunks or roots. It is often implied that both the fibrils and the large axis cylinders, especially those in posterior roots, can serve equally as pain receptors. It should be made clear, however, that axis cylinders cannot be receptors. Pain which radiates down a limb cannot travel by nerve trunks as the pulse travels by arterial trunks.

PRESSURE ON NERVE TRUNKS

Firm pressure or a blow on a nerve trunk is painful, but so is firm pressure or a blow on muscle and other tissues. The testis is more sensitive than a nerve trunk; neural tenderness therefore cannot be due to the axis cylinders it contains. Constriction pain in working muscle is a secondary effect of pressure on motor nerve fibers, which induces painful fatigue.[2] Damage to a sensory nerve does not give referred pain in its field.[3–5]

When the writer's "funny bone" was struck severe pain was felt for five minutes at the site of the blow, spreading six inches below it but not to the hand. In the ulnar field there was a sensation of numbness, then a vivid sense of warmth for 30 seconds, then tingling and a sense of swelling for two minutes; there was slight diminution of touch but no warming of the skin. The radiation of pain did not correspond with that of heat and tingling.

If pressure on nerves were a common

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source of pain, we should expect tumors of nerves to be especially painful. But pain is not a special feature of malignant or benign tumors of nerve trunks.[6,7] Forty-two out of 75 nerve tumors were painless.[8] Forty-seven out of 58 cases of sarcoma of the sciatic nerve were painful.[9] Neuromata of the hand are rarely painful and only occasionally tender.[10] Malignant schwannomas are generally painless, whether in the head and neck[11] or elsewhere.[12] A schwannoma invading the gasserian ganglion caused numbness for two years before it became painful.[13] A lumbar ganglioneuroma in a boy aged 16 presented as a large painless mass.[14]

Case 1.—Ulnar neuritis. No pain in fingers. A man aged 40, who had had several bouts of localized rheumatism, felt pain on the medial aspect of the elbow. The tissues around the medial epicondyle, including the ulnar nerve, became tender. The hand became weak, and the little finger tingled and felt partially numbed. For several weeks he had the usual picture of ulnar paresis. There was severe deep pain along the dorsum of the forearm and in the fifth metacarpophalangeal joint but no pain in the fingers.

The pain of an inflamed nerve did not radiate into the sensory field. Therefore it was due to hyperalgesia of deep receptors in the sheath and not to damage to axis cylinders. The nerve was tender, not because it contained axis cylinders but because it partook of the general hyperalgesia.

THE PAIN PLEXUS

Apart from pain, each sense — touch, heat, hearing, taste, smell, vision — has its own special receptor which is found in only one kind of tissue. Each receptor responds specifically to a single form of energy and ignores all others. Pain is unlike all other senses because it may arise in any kind of tissue, and it can be generated by thermal, chemical, or mechanical stimuli. Naked nerve fibrils and free endings are regarded as suitable receptors because they are found in all tissues and because they could be susceptible to pressure and to other adequate stimuli. Any mechanism which generates pressure anywhere may then be painful.

In favor of the pressure theory we have the common observation that deep tissues are tender to pressure and inflamed tissues to the lightest touch. Hyperalgesic tissues are susceptible to the slightest increase in pressure; a headache or a painful finger may throb with the pulse. When an abscess is incised, pain is relieved at once through lessening of tension.

When tissues are hyperalgesic, however, stimuli which are normally painless summate; otherwise the pressure in the abscess would not have been sufficient to generate pain. Painless distension of tissues by edema, hydrocele, or hematoma is common. Intense pressure on healthy skin or on visceral walls is painless. The alveolar periosteum, which painlessly records intense pressures, is said to contain a special pressure receptor.[15] On the tooth pulp, on the other hand, even the lightest touch becomes pain; pain and pressure must therefore be quite unrelated.

TUMORS COMPRESSING CORD AND NERVE ROOTS

If the pressure theory is true, pressure by tumors on sensory tissue must always cause pain, even as sunshine always causes warmth. There can be no exceptions. If we find that pain is absent from only one in 100 cases of tumor pressing on sensory roots or posterior columns, the theory is disproved and another explanation must be found. But we find

in fact that about one-third of these tumors are not painful at all, and in the others pain is absent for long periods.[16–19]

Case 2.—A man aged 62 first noticed paresthesia in his legs in 1944; this disappeared. In 1945 he felt cramps and in 1946 muscular twitchings in his legs. In 1947 his feet felt numb and his legs became weak. In 1948 his legs became spastic and he had no feeling below the costal margins. A meningioma at the body of the eighth thoracic vertebra was removed, and he gradually recovered power and sensation. At no stage did he feel any pain.

Pain was felt early in 21 of 42 tumors and was absent in 11.[20] Sixty of 300 cases,[21] five of 60,[22] and seven of 36 [23] were painless. It was a late symptom in eight out of 21 tumors in children.[24] Of five tumors compressing the upper cervical cord, one was nearly painless throughout and two were wholly without pain.[25] Pain was the first symptom in only 60 per cent of 179 tumors of the cervical cord.[26] Of six proved cases of intervertebral disk compressing the cervical cord, paralysis was painless in three;[27,28] five out of 11 thoracic disks caused painless paraplegia.[29] Paralysis due to an odontoid tumor caused no pain and was attributed to a degenerative disease.[30] Tumors of foramen magnum are often painless.[31] Only eight out of 15 tumors of medulla oblongata caused headache.[32]

Slowly growing extradural cysts which erode the neural arches of the vertebrae and press on roots usually cause painless paraplegia.[33–40] An extradural hemangiolipoma which destroyed several roots from lower cervical to fifth thoracic level caused painless paraplegia.[41] Five out of nine hemangiomas of epidural space caused little pain.[42,43] Painless paralysis followed intraspinal growth of a hydatid cyst,[44] a cestode cyst,[45] and a teratomatous cyst.[46] A meningioma which destroyed the eighth cervical and first dorsal roots caused painless paralysis of three limbs;[47] two meningiomas pressing on posterior roots caused no pain.[48,49] Intraspinal lipomas are often painless;[50, 51] lipomas of cauda equina usually cause sensory loss without pain.[52] Eleven of 48 cauda equina tumors caused no pain.[53]

Elsberg[54] observed root disturbances in only 15 out of 53 extradural meningeal fibroblastomas and in 15 out of 47 perineural fibroblastomas arising from nerve roots. Local pain in the back was felt in only seven cases in each group; in the majority the earliest symptoms were painless weakness and numbness in the legs. Of 60 cases of dumb-bell tumor of the cord 22 were painful.[55] Rowher[56] saw three cases and two were painless. Other painless dumb-bell tumors have been reported.[57–59]

FACTS VERSUS THEORY

It is important that we should see the force of the logic that a working theory such as this admits of no exceptions. In forming our opinion on these matters we have to be guided by principles which we accept as self-evident. But if one of our guiding principles is erroneous, a whole host of conclusions which spring from it will be faulty.

Current views on pain have never been proved as, for example, the receptor function of the olfactory epithelium has been proved. They have been adopted because they fit in with the general impression that pressure is the effective stimulus for pain. If we keep discovering cases in which pressure does not cause pain, clearly the guiding principle is in error. One fact is sufficient to condemn any theory, no matter how well entrenched. Many of the errors of the present day spring from our unwillingness to

abandon theories which are disproved by facts. Instead we are tempted to support the discredited theory by a supplementary hypothesis which attempts to explain the fact. Claude Bernard[60] said: "When you meet a fact opposed to a prevailing theory, you should adhere to the fact and abandon the theory, even when the latter is supported by great authorities and generally adopted."

PROTRUDED DISK NOT PATHOLOGIC

If we have to abandon the pressure theory of pain, we will inevitably have to abandon many beliefs which depend on it. One of these is the view that pain which radiates in a certain pattern is prima facie evidence of compression of a lumbar root by an intervertebral disk. But we have seen that pain is frequently absent when spinal tumors compress nerve roots.[33–42, 47–59] Of six cervical[27,28] and 11 thoracic[29] intervertebral disks which were observed to press on the cord and cause paralysis, only seven caused pain of any kind. What then are we to think of the intravertebral disk as a cause of sciatic pain? Clearly any pressure which may exist is not the cause of the pain. Evidence suggests that protrusion of a lumbar disk is very common in later years and that it is rarely pathologic.

Even in adolescents small protrusions into the vertebral bodies are common.[61, 62] Later symptomless posterior bulging, sometimes of multiple disks, is frequently seen.[63–66] It occurred in 66 out of 100 cadavers,[67] 32 out of 100,[68] 24 out of 75,[69] 60 out of 95,[70] and eight out of 22.[71] Prolapse of fragments was seen in five[67] to 15[72] per cent. It is less commonly seen because the herniated fragments are often invaded by granulation tissue and soon shrink away.[73–75] In more than one-third of some 200 people who did not have sciatica, lumbar roots were seen at autopsy to be compressed but showed no degeneration.[76,77] Biopsies on patients with sciatica showed that five compressed roots had the same amount of degeneration as five which were not compressed.[78] In the aged the nucleus pulposus frequently disappears without trace.[79] Narrowing of the space may occur in infants;[80] it is seen in normal people as frequently as in those with backache or sciatic pain.[62,67, 81–84] The change is merely degeneration due to senescence.[85–87] Many writers agree that myelography gives no help in diagnosing the state of the disk.

Impartial surveys show that routine operations to relieve pressure on roots have not given good results. Seventy-two out of 200 industrial patients treated by 104 surgeons did not return to work, and the result after three years was good in only 50 per cent.[88] Another group of 235 was equally bad.[89] Of 918 patients surveyed by the American Orthopedic Association, only 65 per cent were satisfactory six years after operation.[90] In England an insurance company assessor[91] and a police surgeon[92] state that the results of modern treatment for lumbago and sciatica are worse than in 1937.

The results of conservative treatment are as good as those of operation; 75 to 83 per cent of patients recover without operation.[93–98] Sprung[99] diagnosed disk disease in 20 per cent of patients with sciatica, and Brav[100] in 36.5 per cent; they operated on only one-third of these. Only five per cent of another series of 6,402[101] came to operation. Bing[102] believes that the disk is responsible for less than two per cent of cases of sciatica.

NEUROLOGIC SIGNS NOT DIAGNOSTIC

When we are operating to relieve pressure on nerve roots, we should expect results to be better if sensory loss had been observed before operation. But there is no difference between those who have and those who have no neurologic signs.[103] Moreover, spontaneous recovery occurs in the same proportion (75-83 per cent) of those with as without motor or sensory loss.[97,98]

Thus the view that sciatic pain is commonly due to pressure on nerve roots is being abandoned in practice. In other regions, somatic pain is usually due to inflammation of articular, ligamentous, or muscular tissue. From a small focus it spreads widely and radiates in constant patterns. Sensory or motor signs mean that nerve fibers have been damaged by the inflammation rather than by compression.

The complexity of the structures in the lumbosacroiliac region suggests that sciatic pain may come from a number of extraspinal sources. That a frequent source is muscle in buttock or thigh can be proved with local analgesia. Important problems which remain largely unsolved are: 1) how to differentiate the two large classes – reflex sciatica from that due to inflammation near the lumbosacral joint; 2) in the second group, how to differentiate involvement of the nerve root from the other causes; and 3) when the nerve root is involved, how to differentiate compression from damage by inflammatory toxins.

SUMMARY

Tumors of nerve trunks or roots or of the spinal cord are frequently painless.

Pressure or tension in tissues is never a primary stimulus for pain; frequently it is a secondary factor in tissues already hyperalgesic.

Lumbar intervertebral disks frequently protrude and press on nerve roots without causing symptoms; prolapsed fragments are often absorbed.

The evidence suggests that pressure on nerve roots is not a common primary cause of sciatic pain.

The list of references documenting this paper is omitted here because of limitations of space, but will be included in the author's reprints.

Nature and Significance of Pentosuria in Neuromuscular Disease

Donald B. Tower, M.D., Ph.D., Edmund L. Peters, B.S. and Milton A. Pogorelskin, B.S.

CLINICALLY DETECTABLE PENTOSURIA was first reported in 1892 by Salkowski and Jastrowitz[1] in a case of morphine addiction. Three types of pentosuria are now recognized. Of these, the type termed chronic or essential pentosuria has been most thoroughly investigated and documented. It is considered to be a benign metabolic disease which is hereditary, affecting Jewish males more commonly,[2] with an estimated incidence of one in ten thousand or less.[3] The pentose excreted has been definitely identified as L(+) xylulose,[4–6] which is excreted in quantities of the order of several grams daily regardless of diet.[7] An association with glucuronic acid metabolism has been strongly implicated.[6,7]

Ingestion of foods high in pentose content, especially fruits, is associated with the type of pentosuria called alimentary pentosuria.[8] The nature and quantity of pentoses excreted have not been well studied, but alimentary pentosuria is of sufficient importance to necessitate institution of fruit-free diets before investigating other types of pentosuria. The wide distribution of pentoses in foodstuffs makes it virtually impossible to devise a pentose-free diet, but apparently fruits are the chief source of alimentary interference.

Toxic or drug-induced pentosuria has never been well defined. Nevertheless, there are a sufficient number of reports to suggest that drugs such as morphine and the antipyretics,[7–9] hormones such as thyroid and cortisone,[10,11] or fever or allergies[9,12] may be associated with transient pentosuria. Relationships of this type of pentosuria to alimentary[8] and to essential pentosuria[7] might be inferred but are certainly not clear.

An association of pentosuria with neurologic disease was suggested in 1907 by Cassirer and Bamberger,[13] based upon a case with transient bilateral quadriceps paresis with femoral nerve tenderness and sensory disturbances, accompanied by pentosuria. Other investigators failed to confirm this observation in similar cases.[14] However, in 1949 Minot, Frank,

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Read in abbreviated form at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 29, 1955.

A portion of these studies were carried out by M. A. Pogorelskin in partial fulfillment of requirements for the degree of Master of Science, Department of Chemistry, Georgetown University, Washington, D. C.

and Dziewiatkowski[15] reported pentosuria in cases of muscular dystrophy, identified by means of the osazone derivative as ribosuria, probably as a phosphate complex. Orr and Minot[12] confirmed this finding for myopathies and presented data suggesting that pentosuria did not accompany other diseases of muscle, nerve, or spinal cord. Thus, the test for ribosuria was proposed for diagnosis of muscular dystrophies.

Although Drew and Selving[16] also confirmed these findings for muscular dystrophy patients, they obtained positive specimens from patients with other neurologic diseases. Using single-dimensional paper chromatography, Matthews and Smith[17] were unable to detect any pentoses in 24-hour urine specimens from a small series of muscular dystrophy patients. In 89 cases of myopathy Walton and Latner,[18] using 24-hour, fruit-free urine specimens analyzed by the method of Orr and Minot,[12] found only 12 positive cases. Thus, Walton and Latner concluded that the test was of no diagnostic value for myopathies.

In the foregoing studies it seems reasonably clear that interference from alimentary sources can be ruled out, since the majority of patients studied were on fruit-free diets and, because of the microscopic quantities involved, it is unlikely that any of these cases had essential pentosuria. Data are insufficient to evaluate possible interference from toxic or drug therapy causes, with the exception of two cases specifically cited by Orr and Minot.[12] That these groups of investigators were in fact dealing with pentoses in the urine is probably correct because the methods employed in processing the urine specimens removed many of the substances which would interfere with pentosazone detection. However, definitive identification of sugars by the osazone method[19] is well known to be difficult and unreliable.[20] Not only are microscopic appearances and melting points of hexosazones and pentosazones very similar, but glucuronides[21] and urates[20] yield similar crystals by this reaction. In addition, it is clearly impossible to state on the basis of osazones alone that the pentose is ribose, since arabinose yields the identical osazone.[22] Thus, the identity of the pentose or pentoses excreted in myopathies remains in doubt.

Of equal importance with identification is the problem of quantitation. Several papers have now appeared indicating that detectable amounts of one or more pentoses were excreted by a variety of human and animal subjects.[10,11,23–28] It can be suggested tentatively that normal human excretion of free aldopentoses is of the order of 6 mg./100 ml. of urine,[28] representing probably a mixture of arabinose, xylose, and ribose.[23,24] These data must be interpreted with reference to recognized types of pentosuria previously discussed. In view of the foregoing, the importance of pentosuria in patients with neuromuscular diseases can hardly be assessed without resort to quantitative data.

Numerous quantitative methods for the determination of pentoses in biologic materials have been developed. Most of the methods are based upon the reaction of pentoses in the presence of heat and acid to form furfural, which can be determined quantitatively.

Classically this is accomplished by steam distillation of a strongly acidified solution[29] and gravimetric determination of furfural in the distillate by precipitation with thiobarbituric acid,[30,31] a method which is specific for pentoses, since hydroxyfurfural formed from hexoses is not precipitated under these conditions.

The method also produces furfural from combined pentoses and in our hands could not be readily adapted to micro-estimations on urine. Various methods for detection of furfural colorimetrically have been developed, including the use of orcinol,[32] phlorglucinol,[33] benzidine,[34] and many related compounds. While these methods are sensitive and simple, they are nonspecific, determining not only total pentoses (free and combined) but also glucuronic acids and other uronides. Since daily excretions of glucuronides may amount to several hundred milligrams,[35,36] serious interference would be encountered from this source. In analyses of some of the 24-hour urine samples used in the present study by the orcinol method,[37] quantities determined could be almost entirely accounted for as glucuronide.[36] In addition it has been reported that appreciable quantities of nucleic acids may normally be excreted in urine,[38] which, as pentose-containing complexes, would also be determined by these methods and represent further source of interference. On the other hand few, if any, of the foregoing methods satisfactorily determine ketopentoses or desoxypentoses, for which special methods are usually indicated.[39–43]

Alternatively, methods of column partition chromatography,[44,45] isolation as benzimidazole derivatives,[46,47] or use of mutant bacterial strains adapted to specific pentoses[48] are available which appear to be specific and possess the added advantage of identification of components in mixtures. These methods are rather complex for routine application to any quantity of specimens. Attempts to adapt the benzimidazole method[46] to quantitative isolation of urine pentoses were unsuccessful on unconcentrated urine specimens for the present study due to the small quantities involved and the interference of inorganic constituents. The well-established methods of paper chromatography of sugar mixtures,[49,50] while most satisfactory for qualitative identifications where available quantities are small, are too time-consuming and too difficult to quantitate[51] to be practicable in this regard.

It is clear that some compromise is necessary in applying a quantitative method to the estimation of small amounts of pentoses in a large number of urine specimens on a routine basis. The method best suited to the requirements of this study appeared to be the method of Roe and Rice,[52] using para-bromaniline for the colorimetric estimation of furfural produced from pentoses by heating urine aliquots at 70° C. in the presence of glacial acetic acid. The milder conditions of this procedure apparently eliminate or curtail most of the interfering substances in biologic materials and thus restrict its action to detection of free aldopentoses. Adoption of this method carries the qualification that not all pentoses (combined or keto- and desoxyforms) would be determined.

Accordingly the method of Roe and Rice[52] for quantitative determination of total free aldopentoses was adopted, supplemented by two-dimensional paper chromatography for pentose identification. Four principal considerations were subjected to investigation: 1) determination of the amounts of pentoses excreted per 24 hours by patients with or without muscle disease; 2) identification of the pentose or pentoses excreted with an estimate of the relative amounts of each type; 3) correlation of the results with clinical diagnoses and status; and 4) examination of the possible mechanisms concerned. The results of these studies comprise the subject matter of this paper.

MATERIALS AND METHODS

Patients for this study were drawn from the wards of the clinical investigations division, National Institute of Neurological Diseases and Blindness. Unless specifically stated to the contrary, all patients were routinely placed on fruit-free diets for at least 48 hours prior to collection of urine specimens. Diets were rigidly supervised during the entire collection period.

In every instance 24-hour urine specimens were collected. All specimens were collected in amber bottles with toluene as preservative (4 ml./bottle) and kept refrigerated during the collection period. Analytic procedures were carried out immediately upon completion of

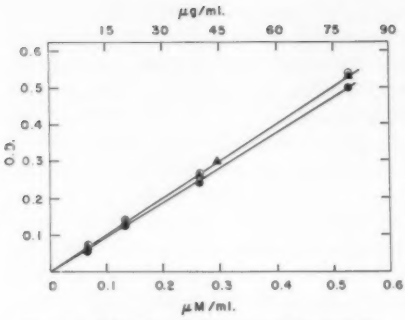

FIG. 1. Calibration curves of optical densities (O.D.) read at 525 mμ for known concentrations of standard solutions of D(+) xylose (○), L(+) arabinose (●), and D(−) ribose (▲), determined by the method of Roe and Rice.[52] 1 μM. of aldopentose = 150 μg.

the 24-hour collection period. These precautions were deemed essential to avoid loss or alteration of carbohydrates present, particularly by epimerization which occurs with the alkalinization of aging of urine.[22,53]

Routine urinalyses for specific gravity, pH, qualitative albumin and sugar, and microscopic examination of centrifuged sediment were carried out on aliquots of at least one 24-hour specimen from each patient studied. In the majority of specimens collected, 24-hour creatine and creatinine determinations were carried out, using the picrate buffer modification of the Jaffe method.[54]

Quantitative method: Aliquots of all 24-hour specimens collected were analyzed for total free aldopentose content by the method of Roe and Rice.[52] Reagents and procedures employed were identical with those outlined by them except that it was found necessary to increase quantities to 3.0 ml. of urine and 15 ml. of para-bromaniline acetate reagent. The para-bromaniline-acetate reagent is extremely caustic. Contact with skin or mucosa must be rigorously avoided. The use of suction-bulb pipetting or similar safety precautions are recommended.

Preliminary treatment of urine, as suggested by Coover and co-workers[10] was not found to be necessary. A water bath thermostatically controlled at 70° C. was used for heating the reaction tubes. Heated tubes and unheated blanks were read against appropriate water-reagent blanks in 25x105 mm. Pyrex cuvettes, using a Coleman Model 8 photoelectric colorimeter fitted with a 525 mμ filter. Each set of assays was read against standard D(−) ribose solutions carried simultaneously through the reaction. Fresh standard solutions were made up daily in distilled water. All results are expressed in terms of D(−) ribose.

Reproducibility and specificity of the method claimed by Roe and Rice[52] were reinvestigated and confirmed. As shown in figure 1, the optical density of the pink color reaction is proportional to concentration over the range of 0.1 to 0.8 μM/ml. tested in conformity with Beer's law. The three naturally occurring aldopentoses, D(+) xylose, D(−) ribose, and L(+) arabinose, give essentially identical optical densities at the same concentration (the slight deviation of arabinose in figure 1 is due to a 5 per cent impurity). Specificity of the reaction for free aldopentoses is shown in table 1. Purity of the D(−) ribose, D(+) xylose, and L(+) arabinose stock standards was checked by determinations of melting point, specific optical rotation, elementary analysis, microscopic appearance and melting points of osazone derivatives, and by two-dimensional paper chromatography. Interference from compounds likely to be present in urine was tested, using concentrations normally expected. Results are shown in table 2. While glucuronic acid and aldohexoses

TABLE 1
SPECIFICITY OF p-BROMANILINE ACETATE REACTION FOR PENTOSES

Pentoses Tested 0.3 μM./ml.	*μg./μM.*	*Per cent O.D. of D (−) Ribose*
ALDOPENTOSES:		
D (−) Ribose	150	100
D (+) Xylose	150	100
D (−) Lyxose	150	100
L (+) Arabinose	150	95+*
KETOPENTOSES:†		
D (−) Ribulose (2-keto)	148	0
D (−) Xylulose (2-keto)	148	0
METHYLPENTOSES:†		
L (+) Rhamnose (hydrate)	182	0
DESOXYPENTOSES:†		
D (−) -2-Desoxyribose	134	0
PHOSPHOPENTOSES:		
Ribose-5-Phosphate (Barium)	230	0

* No pure sample of arabinose available
† Presence in sample verified chromatographically

TABLE 2
INTERFERENCE WITH p-BROMANILINE ACETATE REACTION FOR ALDOPENTOSES

Compound Tested	*Conc. (mg./ml.)*	*Per cent Interference†*	*Comment*
D (−) Ribose	0.045	100	Deep pink
Toluene (preservative)	3.0 ml.	0	
Creatine + Creatinine (each)	1.0	0	
Glutamine + Asparagine (each)	1.0	0	
Desoxyribonucleic Acid (sodium)	8.0	0	
Ribonucleic Acid (sodium)	5.0	0	Turbid, colorless*
Glucuronic Acid (sodium)	0.35	2.5	Pale yellow
D (+) Glucose	0.5	20.0	Yellow-orange
	0.25	10.0	Yellow
	0.1	4.0	Pale yellow
D (−) Fructose	0.25	0	
D (+) Mannose	0.25	10.0	Yellow
D (+) Galactose	0.25	35.0	Orange-pink
D (+) Lactose	0.5	4.0	Pale yellow
Ascorbic Acid	0.1	0	
Hippuric Acid	0.1	0	
Ribose-5-Phosphate (barium)	0.138	0	
after acid hydrolysis**	0.138	6.0	Pale pink
Riboflavin	0.125	0	*
Adenosine	2.0	0	
Glycogen	1.5	0	
Xylan	1.5	0	Turbid, colorless*

† Per cent of O.D. of D(−) Ribose 0.3 μM/ml. (=100%)
* Turbidity or color in unheated blank equal to heated sample
** 2 N HCl at 127° C for 15 min. Ribose unaffected by these conditions.

give detectable colors under these experimental conditions, only glucose and galactose are likely to present an interference problem if present to any extent. Galactosuria is rarely encountered except during pregnancy and lactation, in suckling infants, and in certain types of hepatic disease.[3] Urinary glucose, except in diabetes mellitus or renal glycosuria, usually averages about 10 mg./100 ml. Since qualitative tests for urinary sugar detect 15 to 20 mg./100 ml. or more, a negative qualitative test was accepted as evidence of insufficient glucose to interfere significantly. Only one patient with diabetes mellitus had to be excluded from this study because of marked glycosuria. Recoveries of known amounts of pentoses added to patient urine samples were satisfactory, as shown in table 3.

Paper chromatography: Single- and two-dimensional paper chromatograms were carried out by the method of Partridge.[49,50] Since satisfactory chromatograms require prior removal of salts and other ionic interference from bio-

TABLE 3
RECOVERY OF PENTOSES ADDED TO URINE

Test Solution	*Addition†*	*μM./ml.*	*O.D.*	*O.D. Difference**	*Per cent Recovery*
Urine (J.Sa.)	None	—	0.212	—	—
	D (−) Ribose	0.15	0.364	0.152	98
D (−) Ribose		0.15	0.155		
Urine (R.R.)	None	—	0.316	—	—
	L (+) Arabinose	0.075	0.388	0.072	101
	"	0.15	0.457	0.141	100
	"	0.225	0.520	0.204	97
	"	0.30	0.586	0.270	96
L (+) Arabinose		0.30	0.281		
Urine (F.G.)	None	—	0.233	—	—
	D (−) Ribose	0.15	0.405	0.172	99
	"	0.30	0.585	0.352	101
D (−) Ribose		0.15	0.175		
"		0.30	0.349		

† Weighed amounts dissolved directly in appropriate urine volumes.
* (O.D. urine + addition) − (O.D. urine)

TABLE 4
EFFECTS OF DEIONIZATION ON URINARY PENTOSES

Sample	*Conditions*	*O.D. Sample*	*O.D. Blank*	*Per cent Recovery* †	*pH*
Dist. H_2O	IR-120 + IR-4B	—	0.000		
D (−) Ribose	− − −	0.290	0.000		
	IR-120	0.297	0.000	102	
	IR-4B	0.194*	0.000	67	
Urine (M.Sc.) + D (−) Ribose	− − −	0.590	0.190		
	IR-120 + IR-4B	0.365	0.015	87	
Urine (J.N.)	− − −	0.288	0.100		5.10
	IR-120 +	—	—		±0.75
	IR-4B	0.162	0.030	70	5.48

† Calculated for corrected O.D. = O.D. heated sample − O.D. unheated (blank) sample. For details see ref. 52.
* Using IR-45 O.D. = 0.089 or 30% recovery.

logic specimens,[49] all urine specimens were deionized before being applied to chromatography sheets. One hundred fifty ml. aliquots of 24-hour specimens were run successively through Amberlite IR-120 cationic exchange resin (hydrogen form) and Amberlite IR-4B anionic exchange resin (free base form) in 50 cc. burette columns (bed depth 24 inches) at a rate not exceeding 0.1 ml. per cc. of resin per minute. The first 50 ml. of filtrate from each column were discarded so that only the final 50 ml. from the second column were retained for chromatography. The effects of deionization on pentose content and pH are shown in table 4. Pentose content was determined by the method outlined above. Measurements of pH were made with a Beckman pH meter. After passage through the cationic exchange resin (IR-120), no loss of pentose was observed, but adsorption was 15 to 30 per cent by the anionic exchange resin (IR-4B). Maintenance of an acid pH, as indicated in table 4, is important since strongly basic anion exchange resins have been reported to introduce a lactic acid artefact into the filtrate.[55]

In all chromatograms, a volume of 150 λ (1 lambda (λ) = 1 μl. or 0.001 ml.) of deionized urine aliquots, or standard solutions, were applied to 18x22.5 inch sheets of Whatman No. 1 filter paper in spots not exceeding 0.5 cm. diameter. All chromatograms were run by the descending technic, using water-saturated phenol (100 g. phenol-300 ml. water) as solvent for the first dimension. For two dimensional runs, the sheets, after 18-hour air drying, were run in the second dimension, using n-butanol-acetic acid-water (in proportions of 4:1:5) as solvent. Chromatocabs were used for all paper chromatography.

After 18-hour air drying of all chromatograms, carbohydrate spots were visualized by spraying the sheets with an air-driven atomizer with appropriate reagents and brief heating in a chromatography drying oven.[51] The following color reagents were used: aniline hydrogen phthalate in n-butanol,[50] p-anisidine hydrochloride in n-butanol,[56] and orcinol with trichloracetic acid in n-butanol.[57,58] The orcinol reagent is specific for ketoses,[58] while the other two differentially detect aldoses, ketoses, uronic acids, and other carbohydrate derivatives.[51] Anisidine detects a wider variety of compounds, but for routine use aniline phthalate has proved quite satisfactory. Visual examination (under daylight) of finished chromatograms was routinely supplemented by inspection under ultraviolet light to permit detection of compounds present in minimal concentrations. Mixtures of known concentrations of standard hexoses were invariably run with each batch of chromatograms, and in some instances urine plus standards were run together to verify the identity of spots. On the basis of these studies and the Rf values of the spots in each dimension, the individual carbohydrates were identified.

$$\text{Rf value} = \frac{\text{distance of spot center from point of sample application}}{\text{distance of solvent front from point of sample application where the solvent front distance} = 1.0.}$$

Estimations of the relative proportions of pentoses present were made by the spot area method.[59,60] This method has been recommended where satisfactory separation can be achieved in one dimension and where quantities present are insufficient to assure satisfactory elution for spectrophotometric analysis.[61] The method was applied to the present study

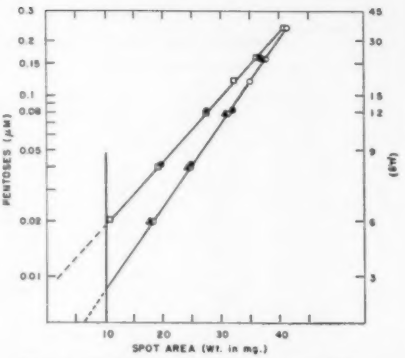

FIG. 2. Calibration curves of spot areas (linear scale) for known concentrations of pentoses in spots (log. scales) on one-dimensional chromatograms. Means of three simultaneous determinations of a series of known concentrations are plotted for D(−) ribose (□), D(+) xylose (▲), and L(+) arabinose (○). Repeat duplicates for ribose and arabinose are also plotted (●). As indicated by the vertical line, the lower limit for accurate determination of spot area (as weight in mg.) was taken as 10 mg.

as follows. Mixtures of xylose, arabinose, and ribose in a series of known concentrations in 150 λ spots equidistant on sheets of Whatman No. 1 filter paper were run with water-saturated phenol as solvent for 24 hours. The air-dried chromatograms were sprayed with aniline hydrogen phthalate in n-butanol. The respective spots so visualized were outlined in pencil, traced onto Whatman No. 1 filter paper, and the traced spots were cut out and weighed to the nearest 0.1 mg. on a semi-micro balance. Spot weights, as a measure of spot area, were plotted against the logarithm of concentration present to construct a calibration curve for each pentose.[59,60] A calibration curve constructed from replicate chromatograms of known standard pentose mixtures is shown in figure 2 with an example of one such chromatogram in figure 3.

From figure 2 it is apparent that, under the experimental conditions employed, arabinose and xylose in identical concentrations exhibit spots of essentially the same size, whereas ribose in the same concentration exhibits a somewhat smaller-sized spot. In fact at concentrations below 0.05 μM, the size of ribose spots is as little as one-half the size of spots for the

FIG. 3. Photographic reproduction of a one-dimensional chromatogram of a series of known concentrations of xylose (X), arabinose (A), and ribose (R) from which spot areas were obtained for construction of figure 2. Concentrations in μg. of respective pentoses in the appropriate spots are given below each vertical row. 15 μg. = 0.1 μM.

two other aldopentoses at the same concentration. For the 24-hour urine specimens, aliquots, deionized as outlined above, were chromatographed in 150 λ volumes in a similar manner, bracketed by mixtures of pentoses of known concentrations. The spot areas of standards and urine pentoses were determined and the relative concentrations were estimated from calibration curves similar to that in figure 2. It is generally accepted that any such method can at best only be a semiquantitation. In order to avoid the problems of differing urine concentrations and direct comparison of one chromatogram with another, which might attach too much significance to actual quantities, all results obtained by this method have been expressed in arbitrary units, referred to arabinose μM/spot estimated = 1.0 unit. (The consistent presence of arabinose in every chromatogram in this study made it a convenient choice as a reference).

RESULTS

1. QUANTITATIVE STUDIES

Determinations of total free aldopentoses excreted per 24 hours were carried out on 230 24-hour urine specimens collected from 55 patients with muscle diseases or no muscle disease. Wherever possible multiple consecutive 24-hour samples were obtained. The results of these determinations, together with other pertinent data, are detailed in tables 5 to 8.

Patients with diseases primary or probably primary in the muscle (the myopathies) are summarized in tables 5

TABLE 5
24-HOUR PENTOSE EXCRETION

Patient	Age (yrs.)	Sex	Wt. (kg.)	Av. Pentose Excretion/24 hr. (mg.)	Av. Pentose Excretion/24 hr. (μM.)	No. of Det'n	Pentose/24 hr. Range (μM.)	Av. 24 hr. Urine Vol. (ml.)	24-hr. Average (mg.) Creatine	24-hr. Average (mg.) Creatinine
MUSCULAR DYSTROPHY										
J.A.	10	M	25	29	193	7	167-214	975	555	195
M.A.	31	M	55	52	347	2	307-387	1145	—	—
Da.B.	13	M	59	63	420	10	307-500	840	740	685
Do.B.	11	M	35	44	294	11	180-367	945	575	535
W.Bu.	37	M	75	79	524	2	500-547	1855	1680	965
†P.Cl.	9	M	29	57	377	2	347-407	1690	535	595
W.Cl.	7	M	19	21	140	4	117-160	600	520	245
P.Co.	15	M	15	38	253	3	240-260	575	650	185
J.F.	13	M	37	53	353	9	267-573	1230	470	265
A.H.	47	F	44	50	333	2	307-360	1255	—	—
J.L.	35	M	55	64	427	5	374-473	1915	1150	275
W.M.	23	M	32	46	304	2	247-360	3110	—	—
E.N.	39	F	47	43	287	10	254-334	1660	810	630
†J.P.	52	M	50	36	240	6	147-327	1865	—	—
R.R.	24	M	61	69	460	5	340-520	1310	—	—
†J.Sa.	11	M	30	47	314	4	247-374	1360	—	—
M.Sc.	52	F	71	69	460	14	320-806	835	—	—
*A.W.	20	M	75	47	314	7	220-586	2445	—	—
†O.Z.	7	M	21	29	193	9	147-347	665	320	200

† Pseudohypertrophic type

* With external ophthalmoplegia

and 6, comprising 31 patients in all. Patients in table 7 were diagnosed as having neurologic diseases, many of which may affect muscles secondarily, whereas the patients in table 8 had no clinically discernible muscle disease with the exception of patient N.A. with disseminated lupus erythematosus which had secondarily involved skeletal muscle. The patients summarized in tables 7 and 8 number 24 in all and have been designated for discussion purposes as having no (primary or intrinsic) muscle disease. Two groups of patients have been assigned rather nonspecific clinical diagnoses. Three patients have been classi-

TABLE 6
24-HOUR PENTOSE EXCRETION

Patient	Age (yrs.)	Sex	Wt. (kg.)	Av. Pentose Excretion/24 hr. (mg.)	Av. Pentose Excretion/24 hr. (μM.)	No. of Det'n	Pentose/24 hr. Range (μM.)	Av. 24 hr. Urine Vol. (ml.)	24-hr. Average (mg.) Creatine	24-hr. Average (mg.) Creatinine
MYOTONIA DYSTROPHICA										
E.G.	43	F	50	61	407	3	384-416	1775	520	775
C.H.	35	M	63	78	520	2	446-593	1250	110	1380
R.H.	41	M	42	84	560	1	—	2520	—	—
S.T.	42	F	52	34	227	3	193-254	1110	270	775
V.W.	47	F	73	54	360	2	327-394	1155	—	—
MYOSITIS OSSIFICANS, PROGRESSIVE										
K.G.	23	M	53	52	347	4	300-433	750	190	1065
MYASTHENIA GRAVIS										
D.Bu.	24	M	70	45	300	2	267-333	840	45	1700
E.J.	37	F	65	85	566	3	394-660	2500	870	1455
†J.N.	47	M	74	64	426	6	367-527	1245	140	1225
MYOPATHY (LATE ONSET), ? CAUSE										
*L.J.	54	F	68	20	133	1	—	1710	1160	475
I.S.	56	F	55	32	213	3	167-240	1550	—	—
L.Sm.	52	F	59	32	214	6	160-240	1460	800	555

† With myositis

* After Cortisone 25 mg. t.i.d. Pentose averaged 406 μM/24 hr.

TABLE 7
24-HOUR PENTOSE EXCRETION

Patient	Age (yrs.)	Sex	Wt. (kg.)	Av. Pentose Excretion/24 hr. (mg.)	(μM.)	No. of Det'n	Pentose/ 24 hr. Range (μM.)	Av. 24 hr. Urine Vol. (ml.)	24-hr. Average (mg.) Creatine	Creatinine
MUSCULAR ATROPHY, ? CAUSE										
J.Ba.	23	F	34	42	280	1	—	1715	—	—
D.H.	33	F	53	42	280	1	—	1450	—	—
†O.M.	33	F	38	49	327	3	300-360	1795	—	—
SPINAL CORD DISEASES*										
L.B.	2	F	13	16	107	2	—	350	—	—
C.Ha.	30	F	63	13	87	1	—	1030	—	—
M.St.	23	F	61	38	253	2	247-260	865	—	—
D.V.	40	M	55	30	200	3	180-220	835	60	1100
MULTIPLE SCLEROSIS										
J.Bi.	35	M	60	42	280	3	240-306	1255	—	—
H.C.	38	M	56	29	193	5	140-246	1130	140	1010
T.F.	50	F	52	38	253	4	187-320	1035	—	—
R.Ro.	51	F	95	21	140	3	127-233	1155	495	795
CEREBRAL SEIZURES										
E.K.	42	M	84	38	253	1	—	2250	—	—
F.P.	38	F	42	30	200	2	120-280	1390	—	—
J.St.	17	M	60	34	226	3	193-280	925	45	1375

† ? Dystrophy

* Diagnoses: L.B.—Spinal Amyotrophy (Werdnig-Hoffmann); C.Ha.—Cervical Myelopathy; M.St.—Prog. Muscular Atrophy; D.V.—Amyotrophic Lat. Sclerosis

fied as myopathies of late onset, cause unknown (table 6), and four have been designated muscular atrophy of undetermined cause (table 7) on the basis of clinical picture, muscle pathology, and electromyography.[62] Difficulties in classifying these patients further at present seemed to warrant separate consideration in subsequent discussions in this paper.

Comparisons of pentose excretions by patients in the myopathy groups (tables 5 and 6) with pentose excretions in the groups with no primary muscle disease (tables 7 and 8) suggest that in the great majority of myopathy patients there is a significantly higher excretion of total free aldopentoses in 24 hours. It should be emphasized that urine volume was not a factor here. Despite variations up

TABLE 8
24-HOUR PENTOSE EXCRETION

Patient	Age (yrs.)	Sex	Wt. (kg.)	Av. Pentose Excretion/24 hr. (mg.)	(μM.)	No. of Det'n	Pentose/ 24 hr. Range (μM.)	Av. 24 hr. Urine Vol. (ml.)	24-hr. Average (mg.) Creatine	Creatinine
OPHTHALMIC DISEASES†										
H.B.	14	F	57	33	220	2	207-233	840	—	—
M.B.	26	F	63	34	226	4	206-246	960	160	1125
C.D.	11	F	32	28	186	4	147-220	710	90	540
F.H.	58	M	67	28	186	10	113-246	1150	80	955
W.H.	30	M	64	35	233	2	219-246	1225	15	1715
S.L.	9	F	26	20	133	2	120-147	575	—	—
E.P.	45	F	—	28	187	9	120-206	1375	80	1075
DISSEMINATED LUPUS ERYTHEMATOSUS										
N.A.	43	F	41	31	206	9	133-274	990	—	—
NO DISEASE										
F.G.	12	M	40	28	183	2	181-184	910	115	575
D.T.	35	M	80	33	220	2	213-226	1175	510	1390

† Diagnoses: H.B.—Chorioretinitis; M.B.—Optic Neuritis; C.D. and F.H.—Granulomatous Uveitis, ? Cause; W.H. and E.P.—Granulomatous Uveitis (Tubercular); S.L.—Granulomatous Uveitis (Toxoplasmic).

TABLE 9
24-HOUR PENTOSE EXCRETION
PER KG. BODY WEIGHT

NO MUSCLE DISEASE				MUSCLE DISEASE			
ADULTS		CHILDREN		ADULTS		CHILDREN	
Patient	μM./24 hr./kg.	Patient	μM./24 hr./kg.	Patient	μM./24 hr./kg.	Patient	μM./24 hr./kg.
M.B.	3.6	L.B.	8.2	M.A.	6.3	J.A.	7.7
J.Bi.	4.7	H.B.	3.9	W.Bu.	7.0	Da.B.	(7.1)
H.C.	3.4	C.D.	5.8	D.Bu.	4.3	Do.B.	(8.4)
T.F.	4.9	F.G.	4.6	E.G.	8.1	W.Cl.	7.4
C.Ha.	(1.4)	S.L.	5.1	K.G.	6.5	P.Cl.	13.0
F.H.	2.8			C.H.	8.3	P.Co.	(16.9)
W. H.	3.6			A.H.	7.6	J.F.	9.5
E.K.	3.0			R.H.	(13.3)	J.Sa.	10.5
E.P.	3.1			E.J.	8.7	O.Z.	9.2
F.P.	4.8			J.L.	7.8		
R.Ro.	2.8†			W.M.	9.5		
J.St.	3.8			J.N.	5.8		
M.St.	4.1			E.N.	6.1		
D.T.	2.8			J.P.	4.8		
D.V.	3.6			R.R.	7.5		
				M.Sc.	(6.5)		
				S.T.	4.4		
				V.W.	4.9		
				A.W.	4.2		
MEAN	3.6 ±0.2		5.5 ±0.74		6.6 ±0.41		9.6 ±0.84

Note: Values in parentheses excluded from calculation of mean (See text)
† For corrected weight of 50 kg.
Values for Muscular Atrophies: J.Ba.—8.2; D.H.—5.3; O.M.—8.6. For Myopathies: N.A.—5.0; L.J.—2.0; I.S.—3.9; L.Sm.—3.6.

to two- or three-fold in volume, pentose excretion remained relatively constant for a given patient from day to day. For reasons to be developed subsequently, these data were recalculated in terms of total free aldopentoses excreted in 24 hours per kilogram body weight. These results are given in table 9.

In calculating the data in table 9 it was clear that extremes of overweight or underweight would give misleading values. Accordingly, the distributions of body weights and of excretions of pentoses per 24 hours per kilogram were examined critically. Those cases which deviated from the mean by twice the standard deviation distribution were excluded from calculation of mean pentose excretions in the table (as indicated by values in parentheses).* The effect of excluding these six cases is actually to underweigh the differences between groups, since inspection of table 9 shows that inclusion of these six cases would alter mean values in opposite directions. As discussed above, the patients with myopathies of late onset and with muscular atrophy of undetermined cause were considered separately. In addition, since the values for pentose excretion per 24 hours per kilogram obtained for children (arbitrarily considered as 15 years of age and under) appeared to be higher than those for adults (17 years of age and over), these were tabulated separately.

When the adults and children with myopathies are compared with the respective groups with no primary muscle disease, marked differences in the means of 24-hour pentose excretion per kilogram body weight are apparent at once. These data and their significance are

*Two patients, Da.B. and Do.B., were also excluded from calculation of mean pentose excretion because clinical and pathologic findings suggested that they could not be considered homogenous with the rest of the patient group.

TABLE 10
SUMMARY OF
24-HOUR PENTOSE EXCRETION

		NO MUSCLE DISEASE		MUSCLE DISEASE	
		Adults	*Children*	*Adults*	*Children*
Number		15 {M-8 F-7	5 {M-1 F-4	19 {M-12 F- 7	9 {M-9 F-0
Mean Age (yrs.)		37	10	37	9
Mean Weight (kg.)		62	34	59	27
Mean Pentose/24 hr./kg.		3.6	5.5	6.6	9.6
Standard Deviation		0.75	1.65	1.68	2.05
Standard Error of Mean		±0.20	±0.74	±0.41	±0.84
Adults vs. Children	S.E.D.	0.77		0.93	
	t	2.47		3.22	
	N	17		21	
	P	<0.05		<0.01	
No Muscle Disease vs. Muscle Disease	S.E.D.			0.46	1.12
	t			6.53	3.66
	N			29	9
	P			<0.001	<0.01

Note: Muscular Atrophies—Av. 7.4 not significantly different from Muscle Disease group.
Myopathies (late onset)—Av. 3.6 not significantly different from No Muscle Disease group.

summarized in table 10. The respective groups are reasonably comparable in terms of number, sex distribution, mean ages, and mean body weights. The differences in means of pentose excretions between adults and children within the same group are probably not significant for the patient group with no primary muscle disease ($P < 0.05$; > 0.02), but appear to be statistically significant for the patients with myopathies ($P < 0.01$). However, comparisons of means of pentose excretions between the respective groups with no primary muscle disease and with myopathies show that the differences are statistically significant for both children and adults. (Comparable results were obtained by statistical analyses of 24-hour pentose total excretions in tables 5 and 6 with those in tables 7 and 8). It is noteworthy that the patients with muscular atrophy of undetermined cause showed an average 24-hour pentose excretion per kilogram body weight which does not differ significantly from the myopathy group, whereas the patients with myopathy of late onset gave an average similar to that for the group with no primary muscle disease. The implications of these latter findings are not clear at present.

From the data in tables 5 to 10, it is clear that there is a significantly higher urinary excretion of free aldopentoses per 24 hours, either total or per kilogram body weight, by patients with progressive muscular dystrophy, myotonia dystrophica, and myasthenia gravis than by patients with other neurologic or non-neurologic diseases. This increased level of pentose excretion is not limited to muscular dystrophies but apparently is also present in muscular atrophy of undetermined cause, in progressive myositis ossificans, and in myasthenia gravis. It was not found in cases of spinal amyotrophy, progressive muscular atrophy, amyotrophic lateral sclerosis, or multiple sclerosis, all of which might be expected to affect the muscles secondarily. With the exception of the patients with myasthenia gravis, who were on neostigmine therapy, none of the 55 patients studied were known to have been on any medication during the period of study. Whether neostigmine can affect

TABLE 11
EFFECT OF ACID HYDROLYSIS ON PENTOSE CONTENT

Patient	*Clinical Diagnosis*	*O.D.*	*O.D. After Hydrolysis†*
J.A.	Prog. muscular dystrophy	[0.167 0.307]	[0.160 0.300]
W.Bu.	Prog. muscular dystrophy	0.420	0.413
W.Cl.	Prog. muscular dystrophy	0.260	0.251
E.N.	Prog. muscular dystrophy	0.142	0.138
E.G.	Myotonia dystrophica	0.300	0.285
J.N.	Myasthenia gravis	0.188	0.185
I.S.	Myopathy (late onset)	0.083	0.085
M.St.	Prog. muscular atrophy	0.212	0.210
R.Ro.	Multiple sclerosis	0.145	0.146
D (−) Ribose	— — —	0.268	0.270

† Conditions: 2 N HCl added to pH 2.5 and heated at 127° C (autoclave) for 30 min. O.D. corrected for changes in volume.

the level of pentosuria could not be determined, since none of the available patients could safely be withdrawn from therapy long enough to conduct the necessary studies. In one patient (L.J. table 6), subsequent cortisone therapy apparently was associated with a tripling of the pentose excretion, a finding consistent with a previous report.[11] The implications of these results in terms of clinical status and possible mechanisms will be discussed below.

The results presented in the foregoing tables also indicate that a small quantity of free aldopentoses is normally excreted by man, even on a fruit-free diet. This finding is in accord with several other reports for man[11,23,24,25,63] and for the rat.[10,26]

In their original paper Minot and co-workers[15] raised the question of excretion of a pentose as a combined compound, probably a phosphate complex, and employed acid and heat hydrolysis for study of this possibility. Of the pentose-phosphates, all but pentose-5-phosphate have extremely labile phosphate groups which would probably be at least partially hydrolyzed even under the mild conditions of the p-bromaniline acetate method.[64] As shown in table 2, ribose 5-phosphate is barely hydrolyzed at all when autoclaved at 127° C. in the presence of 2N HCl to pH 2.5 for 15 to 30 minutes. Since these conditions are much more severe than those employed by Minot and co-workers,[15] it is unlikely that they were dealing with a pentose-5-phosphate.* In order to test whether some other type of pentose complex might be present which would yield free aldopentose under these conditions, aliquots of 24-hour urine samples from nine representative patients were acidified to pH 2.5 with 2N HCl and autoclaved for 30 minutes at 127° C. The results of these experiments are given in table 11. Ribose was unaffected by such treatment and no increase in free aldopentose content of urine specimens was observed under these conditions. Thus, the findings of Minot and co-workers[15] could not be confirmed. Alkaline hydrolysis was deemed impractical since it is well established that sugars are highly unstable at

*It has been brought to our attention that, under the conditions employed here, ribose 5-phosphate may be hydrolyzed and the ribose destroyed, whereas free ribose could be more stable.[91]

alkaline pH and undergo appreciable epimerization and transformation.[22,53]

The possibility that ketopentoses not detected by the para-bromaniline acetate method (table 1) might also be excreted was considered. Evidence against this possibility is discussed below. It may be noted, however, that Futterman and Roe[63] isolated traces of xylulose and ribulose from pooled samples of normal human urine, averaging about 0.027 μM/ml. and 0.006 μM/ml. respectively. The presence of traces of L(+) xylulose in normal human urine had previously been demonstrated by Touster and coworkers.[6] Quantities of this order of magnitude are hardly significant compared to levels of aldopentoses excreted (of the order of 0.2 μM/ml.).

The authors are indebted to Drs. Elizabeth Frame and Chun-Yung-Lee of the Clinical Center, Clinical Pathology Service, National Institutes of Health, for assistance in setting up the Jaffe method and for carrying out a portion of the determinations of creatine and creatinine.

Unless otherwise specified, all carbohydrates and derivatives used were obtained commercially. Samples of authentic D(−)ribulose and D(−) xylulose were kindly donated by Dr. B. L. Horecker, National Institute of Arthritis and Metabolic Diseases. D(−)-2-desoxyribose (California Foundation for Biochemical Research) was provided through the kindness of Dr. B. W. Agranoff, N.I.N.D.B. The sample of D(+) ribose 5-phosphate was generously provided by Dr. S. M. Mann, Nutritional Biochemicals Corp.

The Amberlite resins and suggestions for their use in this study were kindly provided by Rohm and Haas Co., Philadelphia.

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Moebius's Syndrome—
Congenital Oculofacial Paralysis

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MOEBIUS'S SYNDROME, congenital facial diplegia, congenital oculofacial paralysis, and infantile nuclear aplasia are designations which refer to a rare clinical entity consisting of paralysis or paresis of both external rectus muscles and the muscles of the face. Up to the present time less than 100 cases have been recorded in the literature. Often there is weakness or paralysis of the adductor muscles so that horizontal movements of the eyes may be greatly restricted or absent. When adductor weakness is present it is apt to be manifested by a limitation of internal rotation of each eye on conjugate lateral gaze. However, it has been observed that the response of the medial rectus muscles in convergent movements is often diminished and rarely absent.

Associated with these findings there may be a variety of other defects. Cranial nerves in addition to the sixth and seventh are sometimes involved, and deficiencies of chest musculature, club foot, deafness, supernumerary digits, mental defect, and epilepsy have been reported.

Although descriptions of this disorder by von Graefe,[1] Harlan,[2] and Chisholm[3] preceded Moebius's[4] paper, the latter's name has been associated with this syndrome following his complete description in 1888.

Two cases are presented here to illustrate further the hypothesis that the same type of defective development may not only be responsible for the classical features of this syndrome but may also be related to the associated musculoskeletal anomalies.

CASE REPORTS

Case 1.—A 20 year old Negro girl was referred to the neurologic division of the medical clinic of the Vanderbilt University Hospital on December 1, 1954 because she had a generalized convulsion two weeks previously.

Early in infancy it had been observed that she was unable to nurse and had to be spoon fed. Subsequently it was noted that her eyes did not move normally. Two weeks prior to examination she had a generalized tonic-clonic convulsion while asleep. No other history of seizures was obtained. The patient's only sibling, a brother, died at the age of four with a high fever. There was no family history of neuromuscular disease.

On examination she was noted to be a slender, rather dull, girl with a smooth expressionless face. Her mouth was constantly open (figure 1A). Speech was indistinct, especially with respect to labial articulations. Except for minimal movement at the left angle of the mouth, there was a bilateral paralysis of all facial muscles. She was unable to whistle, wrinkle her forehead, or smile. A bilateral Bell's phenomenon was apparent when she attempted to close her eyes (figure 1B). There was no abnormality of the conjunctivas, corneas, irises, or pupils. The lenses and media were clear, and the fields of vision and fundi were not remarkable. Lateral rotation of neither eye was possible when the patient was directed to look to the right (figure 1C) or left (figure 1D),

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Read at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 29, 1955.

FIG. 1. *Case 1.* Facial diplegia with bilateral abducens palsy. *A.* Patient gazing straight ahead. *B.* Attempt to close eyes. Bilateral Bell's phenomenon. Note deviation of mandible to the left. *C.* Right lateral gaze. *D.* Left lateral gaze.

although no diplopia could be demonstrated. All other movements of the eyes were unrestricted. The only other cranial nerve involved was the motor division of the left trigeminal nerve. There was a restriction of lateral mandibular movement toward the right, and her jaw often deviated to the left, especially when she opened her mouth against resistance. There were no congenital anomalies of the musculoskeletal system. Except for a well compensated rheumatic heart disease with mitral stenosis, the examination was otherwise not contributory.

Lumbar puncture yielded clear cerebrospinal fluid under normal pressure with a protein content of 22 mg. per 100 ml. and no leukocytes. Roentgenographic examination of the skull was negative. An electroencephalographic tracing was characterized by slow waves in all leads. This diffusely abnormal rhythm was exaggerated following overventilation.

On psychologic examination her intelligence quotient was 67, but this figure is not very meaningful since her verbal scale was 94 and the performance scale was 44. Her visual-motor integration was particularly affected.

In summary, this patient has a congenital paralysis of the sixth and seventh cranial nerves with partial involvement of the motor division of the left trigeminal nerve. Epilepsy and mental deficiency are also present. There are no musculoskeletal anomalies of the trunk or extremities.

Case 2.—A seven year old boy was referred to the orthopedic surgery clinic of the Vanderbilt University Hospital on May 14, 1953 because of congenital deformities of his lower extremities. Stiffness of the knee joints and malformations of the feet, as well as a bilateral external strabismus, had been present since birth. There had been no difficulty in nursing, and the mother observed no facial abnormality. A speech defect had always been present. About 18 months previously an attempt was made to correct the strabismus. At operation only a few strands of the lateral rectus muscles could be identified. These were cut, but the eyes could not be rotated medially to any degree. The left medial rectus was exposed and was found to be inelastic.

On examination he was observed to be small for his age and exhibited a speech defect characterized by poor enunciation of labial sounds. There was a divergent strabismus (figure 2A), the right eye being displaced more laterally. No motion was present in a horizontal plane on attempted lateral gaze, nor was there any convergence upon near vision. Vertical ocular movements were unimpaired. The pupils and retinas were normal. Although he was able to close his eyes and whistle, there was a paucity of spontaneous facial movements. A weakness of the zygomatic muscles was apparent when he attempted to show his teeth, while the platysma drew the angles of his mouth inferiorly and outward (figure 2B).

There was unyielding fibrous ankylosis of both knees which were fixed in a position of 20 degrees flexion. Cavovalgus deformities were present in both feet. The hips were normal. The muscles of the thighs and calves were wasted, and the usual surface anatomy of the knee joints was not apparent. No bony abnormality was detected on the roentgenogram and the soft tissue shadows were indistinct.

In summary, this seven year old boy has a bilateral facial weakness, paralysis of the lateral and medial recti, and deformities of the lower extremities characteristic of arthrogryposis multiplex congenita (amyoplasia congenita). His only sibling, a ten year old sister, has similar deformities of her lower extremities (figure 3) and also deformities of the hands with flexion webs of the digits (figure 4).

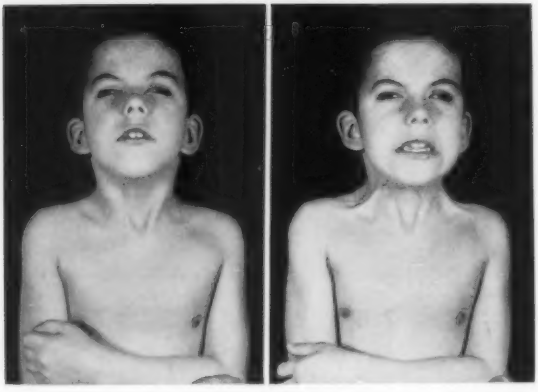

FIG. 2. *Case 2.* Mild facial paresis and external strabismus with complete absence of horizontal ocular movements. *A.* Usual appearance. Note normal upper extremities. *B.* Attempt to show teeth. Note compensatory contraction of platysma.

DISCUSSION

It seems particularly appropriate to quote Wilson's[5] description of this type of facial palsy before further considering the various aspects of this disorder. He wrote: "The clinical picture of complete congenital facial diplegia can not be mistaken; flabby, immobile, and half-open lips combine with obliteration of facial lines to impart to the physiognomy a peculiar mask-like appearance, from behind which issues a voice in monotone, or sounds of laughter, though it perforce remains the picture of gravity."

Henderson,[6] in his comprehensive review of this subject in 1939, tabulated and compared the various clinical features as they occurred in 61 cases. It is customary for the facial involvement to be noticed during the first few days of life because of nursing difficulties and inadequate closure of the eyelids during sleep, followed by an absence of facial movements on crying and smiling. As illustrated by our first case, the mouth is usually open and the lower lip everted. Whistling, wrinkling the forehead, and smiling are not possible in the majority of cases. The paralysis, though generally severe, is often incomplete. The upper facial muscles, such as the frontalis, are more apt to be involved, whereas the muscles which move the angles of the mouth inferiorly and laterally, such as the platysma, are most frequently spared. Both of our patients had speech defects, exhibiting considerable difficulty in labial articulations. As Henderson has pointed out, the characteristic distribution of this palsy contrasts sharply with the usual central and peripheral types and is a rather distinctive feature of this syndrome. Although some writers have elaborated upon the differential diagnosis of congenital facial palsy, it should be easily distinguishable from paralysis of the face due to obstetric trauma because the latter is usually unilateral and unassociated with other palsies.

In Henderson's series approximately 85 per cent of the 61 cases exhibited external ocular palsies and almost all of these included bilateral abducens palsy. There was an ophthalmoplegia in about one-fourth of his cases. In our first case there was an isolated bilateral external rectus palsy, whereas the type of involvement in the second patient, in whom there was absence of horizontal ocular movements, represents an intermediate step between simple abducens palsy and complete congenital external ophthalmoplegia.[7–9] The degree of strabismus which this patient exhibits is not commonly encountered.

Trigeminal nerve involvement, particu-

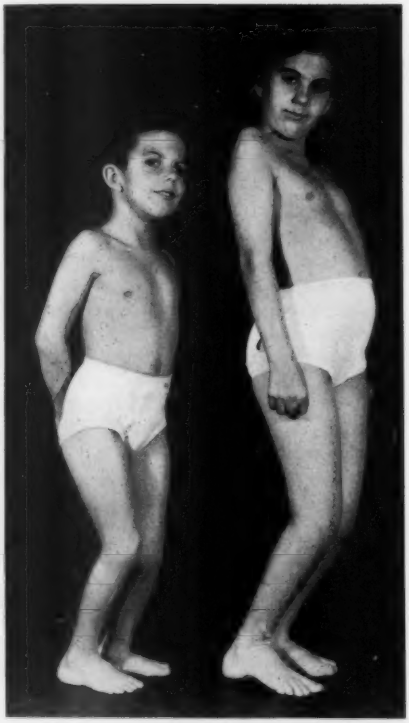

FIG. 3. *Case 2.* Patient and sister displaying identical deformities of lower extremities characteristic of arthrogryposis multiplex congenita. They are demonstrating maximal flexion at the knees.

larly restriction of lateral chewing movements, was reported in four cases of Henderson's series. Van Buskirk[10] in a recent case report, described a nine month old infant with complete paralysis of the muscles of mastication. No masseter muscle was palpable and the jaws could not be closed voluntarily. Our first patient exhibited only weakness of the pterygoid muscles. The mental defect and epilepsy with which she presented have been described in a small number of cases. It is of passing interest that epilepsy was present in von Graefe's patient, the subject of the first report of this disorder in 1875.

The musculoskeletal anomalies seen in many of these patients have been of interest to us because of the deformities shown by the second patient and his older sister, although she had no cranial nerve paralysis. Approximately 35 per cent of the recorded cases of Moebius's syndrome have had a club-foot deformity. Brachial malformations have been almost as frequent and syndactylia has often been noted.

In case 2 a combination of arthrogryposis multiplex congenita and congenital oculofacial paralysis affords an excellent illustration of the possibility that these conditions might have a common genesis. Buchanan,[11] agreeing with Wilson, referred to arthrogryposis as "one of the divisions of the nuclear amyotrophies" along with amyotonia congenita and the progressive spinal muscular atrophy of Werdnig and Hoffmann.

In one of the rare pathologic studies of the condition, Wolf and co-workers[12] recently reported a case of amyoplasia congenita with abnormally small striated muscle fibers and underdevelopment of the anterior horn cells and anterior roots of the spinal cord. They concluded that amyoplasia congenita represented amyotonia congenita plus many other congenital malformations.

Kirby[13] summarized the two theories regarding the etiology of this syndrome: 1) A primary aplasia of muscle, due to a mesodermic defect, the embryonic foundation for the muscles not being laid down, and 2) an ectodermic defect located either at the myoneural junction, the peripheral nerve, or the motor nucleus.

FIG. 4. Hand deformities in sister of case 2.

In a recent report of three cases in the orthopedic literature, Richards[14] concluded that there was not adequate foundation for previous statements that this syndrome might be due to nuclear malformation. He listed several objections which, in themselves, constitute good reasons for continuing to regard this entity as one associated with nuclear hypoplasia.

Most writers on this subject have attributed Moebius's syndrome to a nuclear amyotrophy or dysplasia. Many have alluded to Heubner's[15] necropsy findings of defects in motor nuclei and nerve fibers of the medulla and pons. Murphy and German[16] mentioned hypoplasia of the metencephalon and enlargement of the basal cisterns as pneumoencephalographic findings in their case.

The constellation of defects noted in our cases and those described previously in the literature seem most likely the result of abnormal development of nervous tissue. In view of the distribution of their anomalies, a nuclear hypoplasia of varying degree and distribution constitutes the most popular and reasonable hypothesis.

SUMMARY

Two cases of Moebius's syndrome (congenital bilateral paralysis of the sixth and seventh cranial nerves) are presented.

In one patient this syndrome is associated with arthrogryposis multiplex congenita (amyoplasia congenita). The only sibling of this patient has arthrogryposis but no cranial nerve palsy.

The prevailing hypothesis of nuclear hypoplasia appears to be the most plausible explanation for congenital oculofacial paralysis and the related orthopedic anomalies.

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CLINICAL PATHOLOGIC CONFERENCE

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Presented by *Charles D. Aring, M.D. and Daniel Osher, M.D.*

CASE PRESENTATION

A 36 year old white housewife was admitted to the hospital for the third time in February 1954 because of severe headache, ataxia, and disorientation. She had apparently been in good health until the age of 12, when she developed headaches, double vision, vomiting, and transient numbness in the right upper and lower extremities. Two years before at the age of ten, she had been in an automobile accident and suffered a head injury which rendered her unconscious for approximately 24 hours, but she had no residuals.

When the headaches first occurred at age 12 she was hospitalized for one week but was discharged without treatment because of disappearance of symptoms. At this time, although basically right-handed, she began to write with her left hand because of a tremor of the right hand.

For the next 24 years the patient experienced intermittent attacks of headache, double vision, vomiting, and incoordination of movement. These episodes lasted from one day to two weeks. They occurred infrequently, and between attacks she felt quite well except for persistent unsteadiness of gait and weakness of the right upper extremity.

First admission: In December 1950, after six weeks of extremely severe headaches, vomiting, diplopia, and ataxia, she consulted a physician who immediately sent her to the hospital. No additional pertinent history was obtained. She had undergone no operations, had no other illnesses except for the usual childhood diseases, and experienced no injuries other than the automobile accident mentioned previously. The system review was essentially negative. In 1949 she was delivered of a full-term healthy child. The family history was not contributory.

Physical examination revealed a well-developed, small young woman, alert and cooperative. The temperature was 98.6° F., the pulse 80, and the respirations 20. The blood pressure was 122/80. The positive physical findings were confined to the neurologic examination. Sense of smell was intact. The pupils were slightly irregular but reacted to light and on convergence. Extraocular movements were performed well. There was sustained horizontal nystagmus, most marked on right lateral gaze. Diplopia was present on lateral gaze to the left. The fundiscopic examination revealed slight temporal pallor of the disks; no papilledema was present. An intention tremor and slight ataxia were present in the right upper extremity. Deep reflexes were diminished but present in the right arm. There was no Hoffmann sign. Plantar response was flexor. Slight ataxia on right heel-knee-shin test was noted. There was no impairment of sensation. Romberg was positive.

Lumbar puncture revealed an initial pressure of 375 mm. of cerebrospinal fluid; 12 cc. of clear colorless fluid was removed and the final pressure was 125 mm.; the relaxation was described as "fair." Three lymphocytes and two red cells per cu. mm. were noted. The gold curve showed no precipitation. The Wassermann reaction was negative. Protein was 27 mg. per cent, sugar 51 mg. per cent, chlorides 731 mg. per cent. Because the cerebrospinal fluid pressure was not considered reliable, another lumbar puncture was performed a few days later. The initial pressure was 140 mm. of cerebrospinal fluid and, after the removal of 4 cc. of fluid, the final pressure was 80.

Skull films revealed no bony abnormalities. The pineal gland was calcified and was not displaced. The sella turcica was normal. Other

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laboratory studies were normal. The patient improved steadily and when re-examined by the neurologic consultant three weeks after admission, he noted that most of the neurologic signs and symptoms had disappeared. A few days later she was discharged.

She was followed in the outpatient clinic. Her headaches disappeared completely and she offered no complaints. An electroencephalogram on January 23, 1951 revealed posthyperventilation bursts of high voltage dysrhythmia over both hemispheres. It was considered consistent with possible epilepsy or generalized cortical dysfunction. She was discharged from the clinic in March 1951.

For the next 30 months she remained asymptomatic except for some right-sided weakness and tremor. In August 1953 she again developed headaches and diplopia which waxed and waned. In December 1953 the headaches became intractable and were associated with vomiting, diplopia, and marked ataxia of gait. She was readmitted to the hospital.

Second admission: In December 1953 the neurologic survey revealed probable pallor of both disks, no papilledema, and coarse nystagmus of lateral gaze to both right and left. Pupils were round, regular, and equal in size; they reacted to light and on convergence. Minimal right central facial weakness was noted, as were slurred speech and ataxia of the right upper and lower extremities. There was no gross loss of strength. The appreciation of vibration was diminished in both lower extremities. Touch and pain appreciation were grossly intact. The deep reflexes were markedly hyperactive on the right in both upper and lower limbs. Plantar responses were extensor bilaterally.

Skull films were again negative. No lumbar puncture was performed. She improved gradually on a regimen of bed rest, mild sedation, and analgesics. She was discharged January 16, 1954.

Third admission: She was readmitted in February 1954. During the four weeks following her discharge, the patient's condition deteriorated rapidly. She became completely unable to walk, complained bitterly of headaches, and on the day of admission to the hospital she was aphasic, disoriented, and semicomatose.

At this time in addition to the previous neurologic findings, there were nuchal rigidity, bilateral retinal hemorrhages and papilledema, and decreased hearing on the right. A lumbar puncture revealed an initial pressure of 280 mm. of cerebrospinal fluid; cell count, protein, gold curve, and Wassermann were not remarkable. A ventriculogram was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES D. ARING: This case record depicts clearly the problems of a patient who, beginning at the age of 12, had had episodic crises for 24 years, crises pointing, I believe, to the posterior fossa. I don't see how anyone could have survived 24 years if she had a lesion within the brain itself, so at the outset I am going to say that we are dealing with a mechanical disorder.

To begin in an orderly fashion, there were a lot of general signs pointing to intracranial localization. These were particularly the headache, vomiting, mental signs, and later the signs of increased intracranial pressure that appeared in February 1954. Perhaps the headache may have been a localizing sign, but we don't learn that from the protocol. It might have been possible—and perhaps those who saw her will tell us later—to have depicted this headache or listened to the patient's description of it and got some idea where in the cranium this lesion lay. I am sure that late in the "attacks" it became so severe as to have swamped any localizing attempts.

In any case we have much that points the way to localization. Perhaps most prominent was the ataxia. Certain words are used synonymously for ataxia, I suspect, perhaps tremor and again weakness. As I examined the protocol, there was an instance or two where the writer mentioned weakness but not with much conviction. I believe that this ataxia must have been extraordinarily disabling because it forced the patient to change her handedness at the age of 12. I don't remember ever having heard of spontaneous change of handedness before. I have seen change in handedness in youngsters on the basis of what parents and teachers want, and in later life with the development of hemiplegia and loss of the use of the dominant hand, but I have never heard of a voluntary change in handedness; this must be some indication of the severity of disability in her right upper extremity. Ataxia of such magnitude attracts us without further ado to the posterior fossa, and

this is corroborated by certain other signs such as diplopia and nystagmus, the latter described on one occasion as more prominent to one side, and later equal on gaze to right or to left.

There is a clue, I believe, in the next to last paragraph of the protocol where it is said on the day of her third hospital admission that she was dysphasic, disoriented, and semicomatose. Dysphasia is the word that attracts my attention, which might lead one to think that there was something gone wrong above the tentorium. This word represents a value judgment; one would rather have had a description of exactly what was seen and heard. But since it is put down in conjunction with disorientation and semicoma, it may be that we don't have to weigh this sign too seriously. I am inclined to disregard it. So, from my interpretation of the protocol, I would localize this lesion to the posterior fossa. There is little that would lead me anteriorly; the electroencephalogram showing high voltage dysrhythmia in both hemispheres after hyperventilation wouldn't change my thesis that the trouble was in the posterior fossa.

I want to spend more time on the nature of the lesion, which is the more difficult problem. I think there are more clues that can now be disposed of. There was a head injury at the age of ten years. I am not inclined to believe that this was important. Perhaps it is a universal experience to have head injuries in youth, though they should not render one unconscious for a day. Perhaps it was a severe injury with cerebral contusion, and if so, I can think of few syndromes in our patient that might have followed on such an injury, but more about that in a moment. Another clue is the description of pallor of the optic disks. This leads me to believe that the examiners must have considered multiple sclerosis in diagnosis. Nothing that is very definitive is mentioned about this pallor; it is termed slight and again as probable. I surmise the examiners were straining for a diagnosis and perhaps were projecting on what was a normal difference in color between the nasal and temporal sides of the optic disks. I wouldn't be able to evaluate this finding of an unknown observer without determination of the visual acuity and fields; then one might decide if these disks were normal and the pallor of no clinical significance. One can determine whether optic pallor has any clinical significance with the aid of these adjunctive examinations. Temporal pallor of the disks associated with normal visual acuity and visual fields might be significant clinically, but I would expect it to be very rare indeed.

If this patient does not have intrinsic brain disease, that is, disease of the parenchyma of the brain, what could be the trouble here? Though extraordinarily rare, it is conceivable that certain types of neoplasm might act in this fashion by the now well-known ball-valve mechanism. Sometimes a pedunculated tumor in the third or fourth ventricle shifts its position and somehow obstructs temporarily the pathways of the cerebrospinal fluid, producing an internal hydrocephalus; the latter surely is the condition described in the third hospital admission, an acute hydrocephalic crisis. I can conceive that there might have been such a tumor floating about and periodically lodging to obstruct drainage of cerebrospinal fluid, with recovery of the patient when it dislodged. Such tumors are extraordinarily rare; it would have had to be a benign tumor from the standpoint of histopathology, and, aside from mentioning it, we should consider it no further.

An eighth nerve tumor might be considered in view of the diminished hearing which was found late in the course of this disorder. Acoustic neuromas with onset at the early age of 12 years are rather rare; they usually occur between the ages of 35 and 40 unless they are associated with neurofibromatosis (von Recklinghausen's disease). The latter certainly was not the case here or we would have heard something about the peripheral signs of von Recklinghausen's disease; acoustic neuroma in asso-

ciation with von Recklinghausen's disease almost always has some peripheral manifestations. In these cases, acoustic neuroma is often bilateral and sometimes associated with single or multiple intracranial tumors of other types. We know that the onset of acoustic neuroma is almost always heralded by tinnitus. As the tumor grows the auditory nerve is destroyed, cerebellar signs may occur due to impingement on the cerebellum and its peduncles, and finally obstructive hydrocephalus results. There is no such progression in this patient; also the cerebrospinal fluid protein is normal, and this is almost never the case in acoustic neuroma where the protein is increased. So I would be inclined to rule out cerebral neoplasm because I think of no others that merit consideration besides ball-valve tumor in the ventricle and acoustic neuroma.

As I said at the outset, I think that we are dealing with a mechanical disorder that is periodically inducing internal hydrocephalus. This patient maintained relative well-being between the bouts of hydrocephalus. This is indicated by the fact that she married in 1949 and delivered a normal child, despite this intracranial disorder of no mean proportion which lasted for about 24 years. Nevertheless, the condition is a progressive one in a sense; the bouts seem to become more severe as the years move on, and finally she is in an acute hydrocephalic crisis requiring the attention of a neurosurgeon.

We do not have much aid from the laboratory in our attempts at making an etiologic diagnosis in this patient. The electroencephalogram is abnormal; I have already mentioned it. The cerebrospinal fluid is at one time quite normal; at another the patient has extraordinarily high intracranial pressure – 375 mm. of cerebrospinal fluid. This would corroborate the idea that something periodically dammed back the flow of cerebrospinal fluid and resulted in transiently increased intracranial pressure.

What do I mean when I say that the nature of this lesion is mechanical? I think of three conditions. There is subdural hemorrhage which may reside within the cranium for this length of time; such cases are on record. However, I understand that this woman's mental and physical status between attacks was relatively normal, and I would have expected if she were harboring a subdural hemorrhage in the posterior fossa for 24 years that she wouldn't have functioned so well. I am going to pass along to the next consideration, that of adhesive arachnoiditis. This is an elusive condition, perhaps most often a secondary effect of parenchymatous disease of the brain. It may result after trauma or after low-grade infection, it may represent the residual state of an acute pyogenic meningitis, or it may occur after spinal treatments of various sorts, particularly after spinal anesthesia. She had none of these things as far as the history indicates, except the brain injury at the age of ten. Cases are reported of arachnoid loculations or adhesive arachnitis after trauma, most often about the chiasm and in the cerebellar-pontine angle. Such patients may develop communicating or noncommunicating hydrocephalus due to obstruction of the basilar subarachnoid system. I am not inclined to believe that this condition is operating here because it so rarely develops after head injury – never as far as my personal experience goes – and to have had such a lesion for 24 years is most unlikely.

Now that I've exhausted what I think it is not, I want to spend the remainder of the time talking about what I think this is. The Arnold-Chiari malformation is a congenital disorder in which the inferior lobes of the cerebellum—the tonsils—herniate downward into the foramen magnum; the medulla is usually misshapen and it too passes through the foramen magnum into the upper cervical spine. In infants there is usually an associated spina bifida, although cases have been described where spina bifida was not present. I assume that spina bifida was not present in this patient. In adults the Arnold-Chiari malformation is usually seen in conjunction with bony anomalies of the cranial-vertebral junction. There may be platy-

basia; the foramen magnum is small or misshapen; the atlas is occipitalized and the odontoid process of the axis impinges on the brainstem. This condition may be characterized by neurologic signs referable to the medulla, cervical cord, and lower cranial nerves. There are a number of explanations for the Arnold-Chiari malformation. Perhaps the most common is that the lower end of the spinal cord is fixed in the lower spinal canal, usually in association with a spina bifida, and it cannot migrate upward in the elongating, growing spinal column to the level of L-2 as in the normal. That is, the spinal cord is bound down and cannot move up as it does in the normally developing organism. This traction is transmitted via the spinal cord to the structures in the posterior fossa, and they are pulled through the foramen magnum. This plugs the foramen, interfering with cerebrospinal fluid flow, and hydrocephalus results. All this is compensated for in infancy, but in the aging process increasing density of connective tissue in the posterior fossa further interferes with the outlets of cerebrospinal fluid in the fourth ventricle; this is the type that is associated with spina bifida. In the pathologic examination one sees these elongated tonsils of the cerebellum, and the pia-arachnoid that covers these tonsilar projections is usually thickened and may bind the prolongations of the cerebellum to the brainstem. Hydrocephalus and spina bifida are usually but not always present. The pons and medulla are commonly noted to be flattened or bent or asymmetrical. Hypoplasia of the cerebellum and pons has been noted in the Arnold-Chiari deformity. This syndrome was first described by two German pathologists, Chiari in 1891 and Arnold in 1894. Chiari again described it in 1896 with a beautifully illustrated presentation which has never been improved upon.

Another theory is that the Arnold-Chiari malformation is a maldevelopment of the hindbrain, occurring in utero around the time of closure of the medullary tube or perhaps somewhat later. This is about the third week of gestation and would correspond with the formation of spina bifida and/or myelomeningocele.

Of these mechanical disturbances, I favor the Arnold-Chiari syndrome. I myself have not seen many cases, but we not infrequently find platybasia in the proper roentgen studies of the skull. The condition may remain asymptomatic, particularly in youth, and it may be readily missed unless signs such as spina bifida are present. I needn't detail how a lesion such as this might periodically obstruct cerebrospinal fluid flow and produce hydrocephalus. I can't see how the problem presented by this case could represent anything but a mechanical distortion. I believe this mechanical distortion to be the Arnold-Chiari syndrome. I don't know whether we have been given all the information or not; if the skull plates were entirely normal, it would be a most unusual occurrence. I don't think of many alternatives to this diagnosis; perhaps I would admit of adhesive arachnoiditis.

DR. SAMUEL A. TRUFANT: The student diagnoses are practically all of intrinsic disease of the nervous system. Multiple sclerosis was the final diagnosis by 17 of them; six felt that she had a superimposed tumor, some localizing this tumor, some not. Nine students felt that this was a primary neoplastic process; six of these made a diagnosis of either tumor or acoustic neuroma, three that there was a benign cyst in the third ventricle with ball-valve action. One felt that there was a chronic subdural hematoma in the posterior fossa. Two of the students thought very seriously of mechanical problems, platybasia being mentioned at some length by both of them.

Dr. Aring raised a question about the nature of the headache. The headache was variously described by different observers; in her last two hospital admissions, ataxia, speech difficulty, and the severe headache precluded definition of it. On earlier occasions, it is mentioned that it was all over the head, or frontal, or on one occasion suboccipital. On one occasion in 1950 occipital

tenderness was noted.

The service, even as the students, made a diagnosis of multiple sclerosis until the last hospital admission. However, on several occasions the possibility of mass lesion was raised, neoplasm particularly, but nobody thought strongly enough about it because of the complete disappearance of symptoms.

STUDENT: Are such unilateral cerebellar signs as this woman had seen with the Arnold-Chiari malformation?

DR. ARING: She had persistent unsteadiness of gait, a bilateral sign. I see no reason why one cerebellar tonsil or spinocerebellar tract could not be more severely implicated than the other.

STUDENT: How serious is lumbar puncture in this condition?

DR. ARING: Obviously it was not done during the last hospital stay. I would guess that anything tending to unbalance intracranial equilibrium developed by the patient late in the course of such mechanical lesions might be fraught with a modicum of danger. In any case lumbar puncture should not be done thoughtlessly or in a routine fashion in these conditions.

DISCUSSION OF PATHOLOGY

DR. DANIEL OSHER: The chief problem at the bedside was differentiation between multiple sclerosis and something else; clinically this patient appeared to be a rather typical case of multiple sclerosis. There was variation of opinion about optic atrophy. Roentgen studies of the cervical spine were normal. In December 1950 we experienced what might have been the tip-off to the correct diagnosis, but we followed the rule not to tamper with an improving neurologic patient. At that time this patient was on the service at Jewish Hospital and Dr. I. Mark Scheinker was caring for her. Again the diagnosis of multiple sclerosis had been entertained until a tap was done and an initial cerebrospinal fluid pressure of 375 mm. was found. We thought that perhaps she had a mechanical lesion, just as Dr. Aring has postulated. After a few days spinal tap was repeated and the initial pressure was 140 mm. At that time she was improving rapidly, so she was discharged.

When the patient was seen again in February 1954 there was no trouble in deciding that we had to do a ventriculogram. She had marked papilledema and was going down hill rapidly. There was no platybasia. She had symmetrically dilated lateral and third ventricles, a typical picture of obstructive hydrocephalus from an expanding lesion in the posterior fossa. Therefore, a posterior fossa unilateral exploration was done simply because she had had primarily unilateral cerebellar signs, and this is an easy and safe approach. After the right side of the posterior fossa was entered and an opening made into the foramen magnum, the dura was found to be under markedly increased pressure; therefore, a needle was put into the ventriculogram burr hole and the pressure relieved from above. Then a small opening was made in the right cerebellar hemisphere, just enough to admit the point of a brain cannula, and this was passed inward. At a depth of about 4 cm., heading toward the midline, a cyst was encountered and a gush of yellow fluid occurred. The needle was removed quickly to avoid collapse of the cyst; then a linear incision was made through the dura and the cannula track was followed down to the cyst. Meanwhile a large quantity of yellow fluid was evacuated from the cyst. It contained some red cells, which were most likely due to the trauma of surgery. There was a large cystic cavity deep in the right cerebellum, extending toward the midline. We were able by retraction to thoroughly explore the wall of the cavity and found no tumor nodule. Looking down at the floor of the cyst, I thought that we were probably in the dilated roof of the fourth ventricle, although I am frank to say that I could not identify structures through this small aperture. There was a thin membrane on the floor, and when this was torn I had the impression that clear ventricular fluid poured into

and admixed with the cyst fluid. Microscopic sections taken from the membrane of the floor show what appears to be thickened arachnoid with a bit of round cell infiltration, a chronic arachnoiditis. That is essentially what we found, a benign arachnoid cyst or a benign cerebellar cyst, so we terminated the operation. The patient has recovered completely from the surgery. It is now eight months since the operation. She has lost many of her neurologic signs.

(*To the patient.*) Mrs. C., will you put your arms straight out in front of you? Now touch your nose with the right index finger. You see, there remains a little ataxia. Her eye grounds are normal; her gait is normal. How do you feel, Mrs. C.?

PATIENT: I feel fine.

DR. OSHER: You changed from right to left handedness, didn't you?

PATIENT: Yes, that's right.

DR. ARING: Do you write left-handed?

PATIENT: Yes, I do.

DR. ARING: Do you have headaches now?

PATIENT: Just slight and then only occasionally.

DR. ARING: Where is your headache?

PATIENT: Well, it goes all the way back.

DR. MARTIN B. MACHT: Let me ask you a couple of specific questions. Last fall how frequently were you having your headaches?

PATIENT: Oh, every day, all the time, constantly!

DR. TRUFANT: Looking back on it now, could you describe the headaches you had? Where were they?

PATIENT: They were all over my head.

DR. ARING: Did they start all over?

PATIENT: That's right. And I was sick at my stomach.

DR. OSHER: As far as we can tell, Mrs. C. is relatively completely relieved and we believe permanently so.

DR. MACHT: I wish we had a moving picture record of this patient before operation. It was barely possible for her to walk with assistance. She used a cane, but even with a cane her tremor and ataxia were so pronounced that she couldn't take more than a step or two without help.

DR. OSHER: This patient had a cyst of the cerebellum. Cysts of the subarachnoid space appear to have many causes. This condition is most closely related to chronic cystic arachnoiditis, as was discussed by Dr. Aring. It is possibly a variation of cystic arachnoiditis that may be found elsewhere in the nervous system; the type affecting our patient is more localized. It may occur on the surface of the cerebellum; it may simulate an angle tumor or lie deep in the cerebellum as in this particular case. The etiology is not known and there are various theories in this regard. Some believe that it is a congenital lesion; some believe that it may be related to aberrant choroid plexus; some believe that it may be secondary to infection. Most people believe that these cysts are related to trauma, but some argue against it. This patient did have trauma two years before the onset of her symptoms. Symptoms associated with such cysts usually appear within months or at most several years. Cases have been reported with a history of trauma as long as five or ten years before, where the author tended to discount that history. To my way of thinking this case lends credence to the idea that symptoms may occur for many years after brain injury. Of course we had no proof that this lesion was due to the injury.

These cases have a characteristic intermittent course; they have bad bouts and then recover temporarily. I don't know why our patient improved over and over again. It might be hypothesized that the cyst drained and obstructed periodically; it is possible that it drained into the fourth ventricle because it appeared to go deep at operation. Most of the cases reported in the literature that have been followed over the years have been cured.

DR. MACHT: This patient has been examined monthly since the operation, and in the last three examinations the course has become stationary.

DR. TRUFANT: This is the first time I've

seen this lady since she was in the hospital, and the change in her general appearance is really quite remarkable. I don't believe I would have recognized her. She's put on weight; she looks like a reasonably healthy person now, whereas before she was obviously ill.

We might speculate for a moment about the great difference in pressure readings in the two lumbar punctures in December 1950.

DR. OSHER: It has been noted in some of the case reports that patients were relieved of some of their symptoms with spinal taps. She had this cystic fluid deep in her cerebellum. What caused it, why it came and went, I don't know, and there is no point in speculating any further about it. In every case that I've seen reported, the only time that air studies were done was when papilledema supervened, and that's exactly what happened here.

DR. MACHT: I think that the longest course reported in the literature prior to this one was four years between injury and operation. If our patient's syndrome was dependent upon the antecedent trauma at the age of ten, 24 years passed before she reached surgery. It would seem that her symptoms were identical qualitatively over the 24 years; quantitatively they differed.

DR. OSHER: I don't think anybody should be discouraged about not making this diagnosis. I suppose I'll never make it preoperatively. The important point is that here, as in so many cases that have been diagnosed as multiple sclerosis, a treatable lesion is uncovered eventually.

DR. ARING: It is of some interest that when we have had the happy privilege of correcting a misdiagnosis of multiple sclerosis, the lesion has usually been in the region of the foramen magnum, immediately above or immediately below, in the upper cervical spine, or as here, low in the posterior fossa. One must keep these mechanical disorders in mind; this method is in keeping with an important clinical neurologic tenet, that of striving for a diagnosis of a relievable condition.

DR. JOSEPH SMITH: Was the cyst in relation to the foramen of Magendie?

DR. OSHER: I do not know. Ordinarily we do a bilateral exposure of the posterior fossa. We often remove the arch of the atlas and incise the dura and expose both cerebellar hemispheres and have a complete exposure of the tonsils and the upper spinal cord. This was a unilateral and limited exposure; just a little of the foramen magnum was removed and a little slit made through the dura in order to protect the cerebellum. So where the tonsils went or what the foramen magnum looked like, I don't know; the exposure was too limited for that.

DR. SMITH: Did you have the impression that the cyst went beyond the midline?

DR. OSHER: I had the very strong and certain impression that the cyst went over the midline.

CLINICAL DIAGNOSIS

Multiple sclerosis.

Cerebellar vascular neoplasm (February 1954).

DR. ARING'S DIAGNOSIS

Arnold-Chiari malformation.

PATHOLOGIC DIAGNOSIS

Cerebellar (or arachnoidal) cyst of unknown origin.

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CASE REPORT

Dermatomyositis Following Penicillin Injections

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THE SHARP INCREASE in the number of reports on the collagen diseases in the past ten years has been the subject of considerable comment.[1] Special attention to the problem might be responsible, but another explanation seems more reasonable. The increase in the collagen diseases seems to coincide with the tremendous amounts of newer therapeutic agents injected and ingested, and to which some individuals show a sensitivity reaction. The sulfonamides and penicillin are drugs which can provoke a serum sickness type of syndrome and in some cases this is followed by one of the manifestations of a collagen disease. Rich[2,3] has shown that serum sickness type of protracted anaphylactic hypersensitivity reactions to foreign serum and to sulfonamides can cause destructive vascular lesions in man and animals. We are presenting two cases of dermatomyositis which seemed to follow a serum sickness type of illness and progressed to a full-blown dermatomyositis. In one other case of dermatomyositis there was an exacerbation in symptoms after injections of penicillin.

Case 1.—A 24 year old woman was delivered of a baby on September 3, 1954. Because of an episiotomy she was given penicillin by injection. Ten days later she developed a typical serum sickness-like penicillin reaction with generalized hives and swelling. She was given ACTH daily for seven days and then an antihistaminic with gradual improvement in symptoms. On October 20, she complained of headache and was thought to have a sinus infection. A sulfa drug was administered for three days and stopped when an otolaryngologist found no evidence of disease of the paranasal sinuses. She continued to have frontal headache and on November 5 had diplopia on left lateral gaze. She was extremely tremulous and there was a rash on her forearms and in the axillae. She was hospitalized on November 12.

Neurologic examination revealed coarse nystagmus in all directions. There was a left external rectus weakness. She was extremely tremulous and alternations were done poorly. Heel-to-shin and finger-to-nose tests were performed with a great deal of hesitation and tremor. She walked on a wide based gait and the Romberg sign was positive. All the deep tendon reflexes were hyperactive, but the plantar responses were normal and the abdominal reflexes were active. Sensory examination was normal.

The rash spread to the entire body shortly after admission and she was nauseated. She was confused, but was aware that she was talking to people who were not there. She cried aloud and talked almost incessantly. The suggestion of collagen disease was made and

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steroid therapy instituted on November 16. On November 18 the skin had cleared somewhat, but she was still delusional and hallucinating. A few days later she seemed to be clearing mentally and neurologically and the steroid dosage was reduced. There was a rapid increase in skin symptoms and she said repeatedly that the skin did not itch but felt as though it were burning. A skin and muscle biopsy was done on November 23 and showed the typical lesions of dermatomyositis (figures 1 and 2). Under continued steroid therapy she gradually improved and was discharged on December 4 with slight diplopia and nystagmus.

She was readmitted on December 16 with some vertigo on bending over and turning quickly, and was discharged after spinal fluid and electroencephalographic studies were made. Subsequently she was hospitalized on two other occasions for follow-up studies. At the time of her last admission on April 8, she complained of blurring of vision and examination showed swollen optic nerves bilaterally. Laboratory data are summarized in table 1.

Case 2.—A 23 year old woman was delivered of a child five years ago. She received injections of penicillin and 14 days later she developed joint pain and swelling which subsided in seven weeks. She had several episodes of joint pain and in 1952, following a pelvic laparotomy, she again received penicillin. Her hands and feet became swollen and she had joint pains. In March 1953 she was given gold therapy and developed a painful nonpruritic rash. The joint pains and rash were intermittent until July 1954 when they became constant. At that time she developed urticarial-like lesions, puffiness of the face, and had difficulty in swallowing. She noted some intolerance to sunlight.

TABLE 1
SUMMARY OF LABORATORY DATA. CASE 1.

	Nov. 13	*Nov. 17*	*Nov. 19*	*Nov. 22*	*Nov. 29*	*Dec. 3*	*Dec. 16*	*Jan. 22*	*Apr. 8*
Urine									
Albumin	++	+	0		0	0	0	0	0
Red blood count	5–7	25–30			rare	0	0	0	0
White blood count	15–20	25–50			1–4	rare	rare	0	0
Porphyrins		0							
Culture		0							
Blood									
White blood count	8,500			12,000	14,000	25,000	6,000	9,100	7,900
Per cent eosinophils	8			22	3	1	7	1	9
Sugar	137						106		
Urea nitrogen	6			8		8	13		
Albumin	4.4								
Globulin	1.8								
Potassium	3.9			4.6		4.4		4.4	
Sodium				140		143		144	
Chlor.				103					
Cholesterol		155							
Sedimentation rate	10							22	29
Lupus erythematosus		neg.							
Wassermann	neg.								
Cephalin flocculation			0						
Bromsulfalein			1% ret.						
Cerebrospinal fluid									
Protein	.092%		.172%	.073%	.07%	.073%		.049%	.039%
White blood count	12		203	160	91	48		42	2
Electrocardiogram			normal						
Trichinosis				neg.					
Muscle biopsy				pos.					
Skin biopsy				pos.					

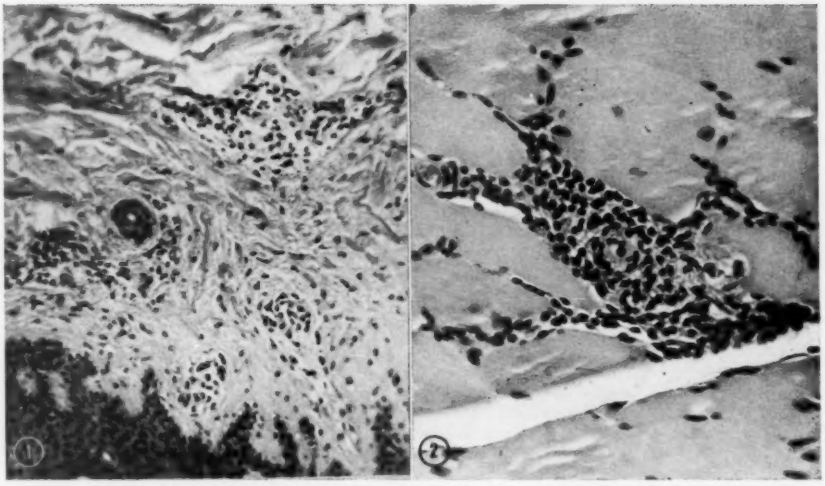

FIG. 1. *Case 1.* Biopsy of skin and left gastrocnemius muscle. There is a dermatitis with perivascular infiltration of mononuclear cells and rare polymorphonuclear cells. In the upper corium the infiltration is more diffuse. There is hyperkeratosis and slight acanthosis with keratotic plugging.

FIG. 2. Muscle biopsy. There is a chronic myositis with focal collections of lymphocytes in the interstitial tissue.

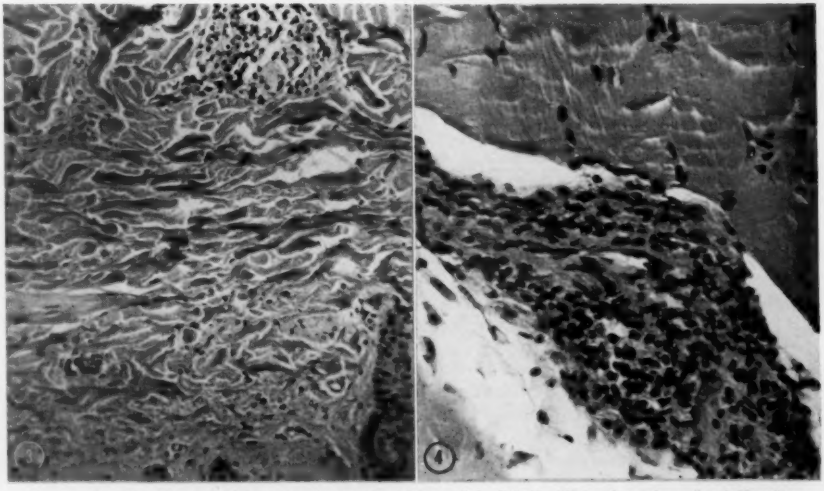

FIG. 3. *Case 2.* Biopsy of skin and subcutaneous tissue — left deltoid. There is perivascular infiltration of lymphoid cells in the skin as well as lymphocytes around a few capillaries in the subcutaneous and fat tissue.

FIG. 4. Muscle biopsy. There is a distinct interstitial myositis with large collections of lymphocytes and a few neutrophils in the interstitial tissue. Some of these cells are around capillaries.

On examination on October 23, 1954 the metacarpophalangeal joints were tender and showed minimal swelling. There was an "urticarial" rash on both thighs. On October 26 there were giant hives and the skin was painful and burning but not pruritic. This skin lesion suggested the diagnosis of a collagen disease and a muscle and skin biopsy were done (figures 3 and 4). These showed the findings typical of dermatomyositis. The patient became increasingly tremulous and developed a delusional and hallucinatory state with marked suspiciousness. This gradually subsided and she improved. The laboratory studies showed a normal blood count and urine. The blood sedimentation rate was 42 mm. in one hour. A sternal puncture on October 30 showed cells resembling lupus erythematosus cells and steroid therapy was begun.

A report from her doctor on March 25, 1955 indicated that she was doing poorly, with innumerable areas of collagen swelling, dislocation of small joints, and much pain. Steroid therapy was not effective in relieving her symptoms.

Case 3.—A 42 year old woman had an episode of fever and eosinophilia 14 years ago. At that time polyarteritis and trichinosis were considered. She had three pregnancies and eight spontaneous abortions. In 1950 a hysterectomy was performed, and in February 1951 she had an acute illness with joint pains, palpitation, dyspnea, and cyanosis. The P-R interval was prolonged. She was treated with ACTH. In October 1952 she complained of pain in the shoulders and in the muscles of the arms and forearms. After Thanksgiving she had pelvic surgery and penicillin was administered. There was a marked increase in joint and muscle pains. In January 1953 a muscle and skin biopsy was done and showed a typical dermatomyositis. Since then she has been on steroid therapy with slight relief and has required Demerol for control of pain. She had several seizures and is on anticonvulsant medication.

COMMENT

The relation between the onset of symptoms and an injection of an antibiotic seems quite clear in these cases. All patients exhibited definite allergic responses to penicillin in the form of a skin reaction and swelling. Whether it actually initiated the dermatomyositis in the cases presented is not definite. However, penicillin played some role in bringing out the collagen disease in two cases and in the third case there was a definite exacerbation in the symptoms. The finding of L.E. cells in case 2 may elicit some discussion regarding classification. Although the symptoms were referred to muscle, skin, and joints, this case might be diagnosed as systemic lupus erythematosus. L.E. cells have been found in penicillin reactions by Walsh and Zimmerman.[4] It is our feeling that the classification depends on the main symptom, in this case the muscles and skin.

The delirious reaction was a prominent feature of the two cases. The type of delirium was that ordinarily seen in toxic reactions and there were the usual tremulousness, apprehension, and auditory and visual hallucinations appearing in the background of occasional good contact with the environment.

The type of skin lesion deserves attention. It may best be described as a burning type of reaction rather than a pruritic lesion. The height of the skin lesion coincided with the delirious reaction.

The other manifestations of central nervous system involvement in case 1 were ocular muscle palsy, nystagmus, and optic neuritis. The pleocytosis and increased cerebrospinal fluid proteins were further evidence of involvement within the nervous system. Bauer[5] presented a small group of cases with reference to studies of the spinal fluid and the electroencephalogram. Elkington[6] also noted some material with signs of involvement of the nervous system as well as the muscles. Although photosensitivity has been considered a part of the lupus erythematosus symptomatology, it has been mentioned in cases of dermatomyositis.[7]

Sensitivity reactions with skin and muscle changes have been reviewed by Wedgewood, Cook, and Cohen[8] in a series of cases of dermatomyositis in children. In two of these cases there were manifestations of sensitivity to sulfadiazine and penicillin.

Sensitivity to salicylates, vaccination, trauma, exposure to physical agents, and viral[9] or bacterial agents have been described.

The finding of polymyositis and carcinoma has been emphasized.[10]

Treatment of these patients has gone through many phases. Prior to the use of steroids, therapy consisted of physical therapy, heat, salicylates, and hormones. None seemed effective, although the disease has a tendency to be cyclic in nature. Steroid therapy has produced a remarkable advance and results in clearing of the skin lesions and lessening of the inflammatory process in muscles. Failures with steroid therapy have been reported. The newer steroids have been used in one case and seem valuable because of the fewer side reactions.

SUMMARY

A collagen-like disease can be produced experimentally in an animal by creating conditions similar to those obtaining in serum sickness in humans. In man collagen disease can be a manifestation of a sensitivity reaction. Penicillin may evoke a serum sickness type of reaction with lupus erythematosus cells, polyarteritis, and dermatomyositis. Two cases are described in which penicillin seemed to initiate a train of events leading to the syndrome of dermatomyositis, and another case in which exacerbation in symptoms followed injections of penicillin is reported.

We wish to thank Dr. L. Maxwell Lockie and Dr. Marshall Clinton for the use of their case material.

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■ We pass now to the transmission of the orders of the will to muscles through the spinal cord. It is by far very much more difficult to determine what are the parts of this organ employed in voluntary movements than to find out what are those through which the sensitive impressions are transmitted. I have long been in doubt in this respect, and even now, after having carefully watched a great many animals, on the spinal cord of which certain alterations had been made, and after having read a great many pathological cases, I still hesitate as regards various points. I will try in this lecture to show what seems to be positive, and I will also point out some of the questions that seem not to have yet been solved.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

CASE REPORT

Hyperplasia of Leydig Cells in Chronic Paraplegia

John D. Keye, Jr., M.D.

THE ASSOCIATION of testicular atrophy and Leydig cell hyperplasia with traumatic or degenerative lesions of the spinal cord has received scant attention. Cooper and co-workers[1] mentioned that the interstitial cells of the testis may become abundant following spinal cord diseases and testicular atrophy, and Horne and co-workers[2] recorded this phenomenon in one of 18 paraplegic patients. The relative paucity of reports dealing with this subject forms the basis for this presentation of an illustrative case.

CASE HISTORY

A 45 year old Negro male was hospitalized in January 1955 for evaluation of his complaints of inability to walk without crutches and urinary dribbling for 15 years.

He related that in 1940, while sawing wood, his legs felt weak and knees began to shake. The next day he could not walk and noted a sensation of bladder fullness, as well as urinary and fecal incontinence. Next he discovered loss of sensation in the lower extremities. His symptoms did not progress further. After one year he learned to ambulate with the aid of crutches. Penile erections occurred sporadically until 1948 when they ceased.

Physical examination revealed a well developed and well nourished Negro man who did not seem ill. His temperature was 37.4° C., pulse 84, respirations 18, and blood pressure 110/80. Healed burn scars and indolent ulcers involved the skin of both lower extremities. The urinary bladder was distended and slight tenderness was noted in the suprapubic region. Other findings included a left indirect inguinal hernia, small testes, and a slightly enlarged, smooth prostate. Examination of the head, eyes, ears, nose, throat, heart, and lungs was negative.

Neurologic examination disclosed a spastic paralysis of the lower extremities and hypalgesia extending up to the midthigh bilaterally. Muscular atrophy of the lower limbs was minimal. Vibratory sense was absent over the malleoli and patellae. Tone of the rectal sphincter was normal. Signs of abnormal cerebellar function were absent, and tests of cranial nerve function were normal. The spinal fluid was clear and its opening pressure and manometrics normal.

Laboratory studies of the spinal fluid disclosed a colloidal gold curve of 443210000, protein 31 mg. per cent, chlorides 124 mEq./L., and sugar 67 mg. per cent. The spinal fluid Wassermann was negative. An albuminuria of 3 plus was found. The urinary sediment was packed with white blood cells, and many cocci and a few bacilli were observed in a smear stained with methylene blue. A culture of the urine grew *Proteus vulgaris* and nonhemolytic staphylococcus. A complete blood count and blood chemistry studies were within normal limits, and serologic cardiolipin and Kolmer tests were negative.

Roentgen examination included myelograms which did not show any defect or obstruction. Intravenous pyelograms showed prompt filling, with normal pelvis and collecting system bilaterally, marked ureterectasia on the right, and

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a ureterocele measuring 2 cm. in diameter involving the right ureter. Arising near the left ureterovesical junction was a 3 cm. diverticulum.

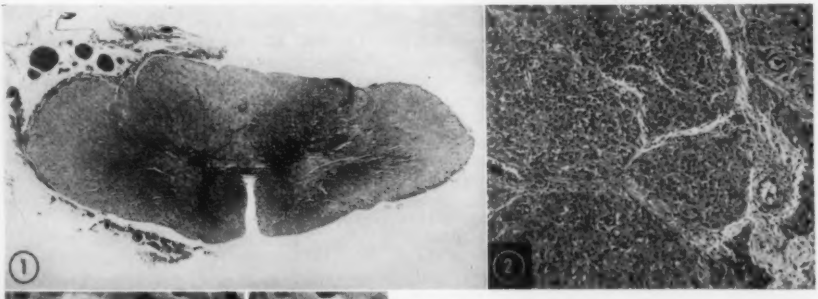
Hospital course. The preliminary clinical impressions were spastic paralysis and sensory loss of the lower extremities, probably due to old hematomyelia, cord bladder, hydroureters, ureterocele, diverticulum of the urinary bladder, hyperplasia of the prostate gland, and urinary tract infection.

The residual urinary volume was found to be 400 cc. He was treated with Gantrisin and the urinary tract infection cleared satisfactorily. It was felt that a resection of the prostate would diminish his large residual urine volume and minimize recurrent infection of the urinary bladder. A transurethral resection and meatotomy were performed under sodium Pentothal anesthesia. At completion of this procedure cardiac arrest occurred. No cardiac beat was detected after thoracotomy; cardiac massage did not revive the heart beat, and only after the intracardiac injection of 10 per cent calcium chloride could the pulse be felt and the systolic blood pressure be detected at 80 mm. Hg. The elapsed period of asystole was greater than ten minutes. Postoperatively he was decerebrate and did not respond to grossly painful stimuli. Cheyne-Stokes respirations evolved and he expired on the morning of the day following operation.

The final clinical impression was extensive cerebral damage due to cerebral anoxemia incident to cardiac arrest during surgery.

Postmortem examination was performed five hours and 40 minutes after expiration. The spinal cord extending from the fourth through sixth thoracic segments was very narrow, and no trace of the normal gross architecture was seen in transverse sections in this area. The cut surface of the small, atrophic testes was yellow-brown and the consistency firmer than usual. When grasped with a forceps the seminiferous tubules did not string out. The right testis measured 3.5x2.5x2.5 cm. and the left 3x2.5x2 cm. in their greatest dimensions. The urinary bladder contained 800 cc. of clotted blood and urine, and was dilated to the level of the umbilicus. A thin layer of fibrin and clotted blood was adherent to the prostatic bed, and lateral to the left ureteral meatus was a diverticulum of the urinary bladder. Slight hydronephrosis of the right kidney and dilatation of its ureter were present. The sac of the left indirect inguinal hernia contained omentum. Other findings included slight dilatation and hypertrophy of the heart and congestion of the lungs and liver.

Microscopic examination of the narrowed



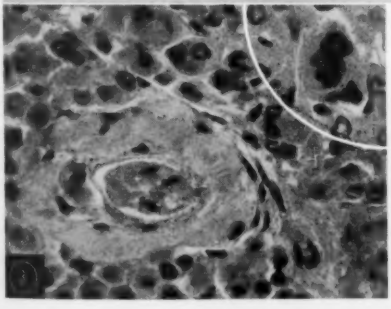


FIG. 1. Low power photograph of thoracic spinal cord at upper extremity of lesion. There is pallor of posterior and lateral columns with gliosis, proliferation of blood vessels, and loss of myelin in these areas. Weil stain.

FIG. 2. Low power photomicrograph which shows nodular character of Leydig cell hyperplasia and compression of the atrophic tubules (lower right) and of blood vessels. Hematoxylin-eosin stain.

FIG. 3. High power photomicrograph of atrophic seminiferous tubule (center) possessing remnants of the germinal epithelial lining and surrounded by polygonal Leydig cells. A giant interstitial cell is shown in upper right (inset). Hematoxylin-eosin stain.

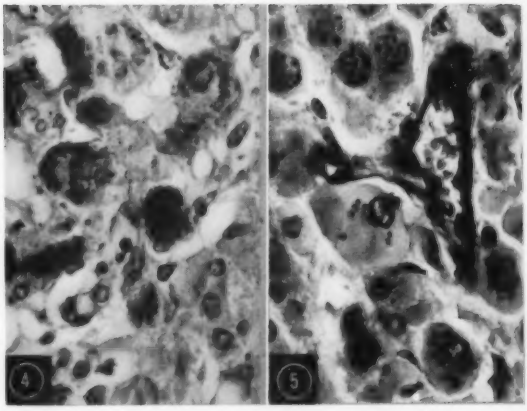


FIG. 4. High power photomicrograph demonstrating variable number of deep purple intracytoplasmic granules in Leydig cells stained with aldehyde-fuchsin.

FIG. 5. High power photomicrograph illustrating the deep red intracytoplasmic granules of intertsitial cells stained with periodic acid Schiff.

segment of the thoracic spinal cord disclosed a gliosis and demyelinization with fibrous intimal thickening of small blood vessels, particularly in the posterior and lateral columns (figure 1). No hemosiderin pigment or thrombi were found. Above this lesion there was demyelinization of medial portions of the fasciculus gracilis, while below it demyelinization was observed in the lateral corticospinal tract. The inner one third of the cerebral cortex in all areas appeared less compact than usual. Neurons there were shrunken, somewhat pyknotic, and many were surrounded by a clear space. Tiny petechiae were fairly numerous, and clumps of leukocytes were adherent to the intimal lining of many small blood vessels.

The testes were histologically similar. Walls of seminiferous tubules were hyalinized, possessed little or no germinal epithelium, and were shrunken and atrophic (figure 2). Nodules of polygonal interstitial cells compressed, but did not invade, the seminiferous tubules and blood vessels (figure 3). Cytoplasm of the Leydig cells was uniformly eosinophilic and sometimes contained golden-brown pigment granules. Their nuclei were large, spherical, or oval, and contained one or more nucleoli. Giant cell forms were present but not numerous (figure 3, insert). Mitoses were absent although there was considerable variation in nuclear size. Cytoplasmic granules stained a deep purple with aldehyde-fuchsin (figure 4) and an intense red with periodic acid Schiff stain (figure 5). A small amount of cytoplasmic lipid substance appearing in coarse and finely dispersed globular form was observed in frozen sections stained with oil-red-o and sudan IV. Rare intracytoplasmic crystalloids were found. In the epididymis of each testis were small granulomatous foci with scattered giant cells, a prominent lymphocyte infiltrate, and several obliterated tubules. Acid-fast stains failed to demonstrate any organisms.

Additional microscopic observations included an early bronchopneumonia, a slight degree of central congestion of the liver, and a few clumps of polymorphonuclear cells beneath the epicardial surface of the heart. The kidneys, spleen, pancreas, adrenals, thyroid, and pituitary were normal.

The final anatomic diagnoses were segmental gliosis, demyelinization, and atrophy of the spinal cord with fibrous intimal thickening of small arteries and arterioles in the fourth through sixth thoracic segments, testicular atrophy, advanced hyperplasia of the interstitial cells of the testes, early anoxic cerebral degeneration, bronchopneumonia, congestion of the lungs and liver, right hydroureter, and hydronephrosis.

DISCUSSION

Detailed studies of the deranged endocrinologic, metabolic, and neurophysiologic functions of paraplegic patients have been presented by Cooper and Hoen[3] and by Talbot.[4] In addition to neuromuscular dysfunction, the observed changes are gynecomastia, loss of sexual potency, testicular atrophy, proteinuria, creatinuria, lowered basal metabolic rate, and impaired liver function. Apparently most of these latter abnormalities may reverse eight to ten weeks following injury, although Cooper and associates[5] have emphasized that the

use of testosterone has considerably reduced the morbidity and speeded recovery during the acute period of injury in males.

The significance of gynecomastia in paraplegic males is not clear and perhaps is related to the transitory impaired liver function (the incidence is said by Cooper and Hoen[3] to be approximately 20 per cent, while Talbot[4] noted an incidence of approximately 1 per cent).

Investigation of the loss of sexual potency involves multiple and complex considerations. The latter include inability to achieve an erection, pain, debilitation, failure to ejaculate, lack of libidinous sensation, and altered psychosexual activity.[4]

Testicular atrophy is said by Cooper and Hoen[3] to occur in over 50 per cent of paraplegic males. Evidence obtained both from experimental animals and observations made on the gonads of paraplegic men indicates the importance of an intact pituitary-hypothalamic-spinal-peripheral autonomic pathway. The hypothalamic-gonadal pathway in the spinal cord has not yet been identified. The existence of a higher center that may influence the maturation of the seminiferous tubular epithelium has been suggested by Bustamente,[6] who consistently observed gonadal atrophy (in male and female rabbits) following localized lesions of the tuber cinereum. In this instance the gonadal atrophy was not affected by the administration of pituitary gonadotropic hormone. McCullogh and co-workers[7] described the frequent occurrence of testicular atrophy in patients with various organic lesions of the pituitary. Bors and associates[8] suggested that a neurologic basis for testicular atrophy exists in the paraplegic due to secondary hyperthermia and hyperemia incident to loss of sympathetic innervation. This conclusion followed the observation that impairment of sympathetic distribution to the trunk and lower extremities (as determined by impaired sweating in a group of paraplegic patients) was closely correlated with the altered testicular structure as determined by biopsy studies. It is felt that the extreme Leydig cell hyperplasia seen in the present case is analagous to that known to occur in cryptorchids where the temperature environment of the testis is such that seminiferous elements atrophy and interstitial cells flourish. Kuntz[9,10] and Kuntz and Morris[11] eliminated the sympathetic nerve supply to the testes of dogs and cats and observed degeneration of seminiferous epithelium followed by hyperplasia of the interstitial cells. Anatomic observations in experimental animals[9–11] and in human stillborn infants[12] indicate that the testis is innervated solely by sympathetic fibers which accompany blood vessels.

"Neurogenic hypogonadism" has been observed in degenerative lesions of the spinal cord as well as following trauma, and has been reported in a patient with Freidreich's ataxia and two others with syringomyelia.[1] The lesion of the thoracic cord in the case presented is thought to have resulted from occlusion of a spinal artery, although this could not be definitely ascertained.

Numerous authors have discussed the hormonal derangements in paraplegic patients. The urinary 17-ketosteroid excretion has been variously reported as low,[13] normal,[14] and normal to high.[8] Bors and coworkers[8] were unable to correlate either the testicular biopsy findings or the level and extent of the cord lesion with the 17-ketosteroid excretion. McCullogh and associates[7] stated that, in their group of patients with pituitary lesions, the urinary 17-ketosteroid excretion proved an unreliable index of Leydig cell activity, and that low excretion of 17-ketosteroids was seen only in patients who evidenced adrenal cortical insufficiency in addition to Leydig cell failure.

Urinary gonadotropins have been said to be "low normal" in paraplegic patients, and McCullogh's group[7] felt that, in individuals with pituitary lesions, the degree of tubular damage was related to the deficiency of pituitary gonadotropin excretion.

Levels of urinary estrogens have been found elevated in a group of paraplegic individuals,[8] but this observation could not

be correlated with testicular biopsy studies. It is evident that the relationship of endocrinologic disturbances in paraplegia to testicular atrophy and interstitial cell hyperplasia is not understood.

The observed epididymitis was considered as a possible explanation of the testicular atrophy, but it was concluded that the degree of involvement was not significant. Support of this view was found in the report by Stemmermann and co-workers[15] of the histologic observations in autopsied paraplegic patients and from testicular biopsies in living paraplegics in which no correlation was found between the presence of maturation arrest and epididymitis.

SUMMARY

A case is presented of testicular atrophy with a remarkable degree of Leydig cell hyperplasia occurring in a 45 year old man who was paraplegic for 15 years. The significance of an intact neural pathway from the pituitary and hypothalamus to the gonads is discussed and the various hormonal factors reviewed.

The author wishes to thank Dr. D. E. Smith for assistance in interpretation of the neuroanatomic findings, Dr. P. M. Hartroft for preparation of the photomicrographs, and Mr. V. W. Fischer for translation of the German reference.

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CASE REPORT

Tumor of the Foramen Magnum

Winchell McK. Craig, M.D., Joe R. Brown, M.D., and John E. Osborn, M.D.

OCCASIONALLY a patient presents unusual neurologic findings and a desperate physical status, but his response to treatment is amazingly gratifying.

REPORT OF CASE

A male, white radio technician, 23 years of age, was admitted to hospital under our care in January 1953. Complaints were of occipital headaches, loss of sensation below the neck, and inability to move any extremity.

The patient had been kicked in the occiput by a horse at the age of eight years. Although he had been unconscious for several minutes and unable to see for a half hour, he had recovered in a few days without known residua.

In 1949 left occipital and parietal headaches had developed. These had been intermittent and mild until 1951 when they became severe and awakened the patient from sound sleep at night. During the day the headaches were intensified by exertion and by standing or sitting upright. The patient thought that chiropractic adjustments had produced improvement for a while.

In November 1951 headaches were severe enough to cause the man to quit work; about this time he noticed loss of pain and temperature sensation in the right lower extremity. Roentgenograms of the head and cervical portion of the spinal column, taken by his physician, gave evidence of apparently normal conditions. Pneumoencephalographic and spinal fluid studies in December 1951 gave no evidence of anything abnormal.

By January 1952 the patient noticed loss of pain and temperature sensation on the entire right side of the body below the neck. About this time extension of the neck produced a feeling of numbness of the entire body from the neck down, and consequently, the patient was obliged to keep his head somewhat flexed. About February 1952 a chiropractic adjustment was followed by subjective numbness of the entire body and weakness of the right hand. Subsequently anorexia, nausea, and occasional vomiting developed. In July 1952 the left arm became progressively weak and this was followed by weakness of the left and later the right lower extremity. About this time complete sensory loss of the entire body and vesical incontinence developed. The man had pneumonia in December 1953. He was almost completely quadriplegic, with sensory loss below the neck and loss of sphincteric control for about four weeks before admission.

On admission the patient was quadriplegic and was breathing with accessory muscles of the neck.

The strength of the sternocleidomastoid muscles was graded −1 on a scale wherein 0 represented normal and −4 represented no voluntary contraction. Sensory examination of the face will be described later. In other respects examination of the cranial nerves gave negative results. The muscle-stretch reflexes were markedly exaggerated throughout all four ex-

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tremities; the superficial abdominal and cremasteric reflexes were absent, and the Babinski sign was positive bilaterally. All extremities were markedly spastic. Except for trace contractions of a few muscles in the right arm and in both legs, voluntary movement was absent. Voluntary contraction of all muscles was graded either —3 to 4 (trace) or —4 (none). Superficial sensation at the level of C-1 and below was completely lost. Vibratory and joint sensations were absent in all four extremities.

Sensory examination of the face was particularly interesting. Touch sensation was normal over the entire distribution of the trigeminal nerve. Pain and temperature sensations were lost from the boundary of the area of loss in the distribution of C-1, C-2, forward to the middle of the forehead, middle of the cheek, and lower portion of the chin, bilaterally. In a concentric circle forward from this there was a narrow zone of 50 per cent loss of pain and temperature sensations. Sensory perception was normal in the region around the eyes, nose, and mouth (figure 1).

In the course of general physical examination, the patient was supported in a sitting position to allow adequate examination of the thorax. He ceased to breathe. He was given artificial respiration and then was kept in a respirator until his own breathing again became adequate.

Laboratory examinations included roentgenograms of the head, thorax, and cervical portion of the spinal column, which did not give evidence of anything abnormal. The concentration of hemoglobin was 13.4 gm. per 100 ml. of blood; erythrocytes numbered 3,710,000, and leukocytes 6,100 per cubic millimeter blood. The erythrocyte sedimentation rate was 92 mm. per hour (Westergren). In the urine were erythrocytes, grade 1, leukocytes, grade 3, and albumin, grade 2.

On the basis of the history and the neurologic examination a clinical diagnosis was made of tumor, possibly of dumbbell type, located at the foramen magnum or high in the cervical portion of the spinal column. The dissociated sensory loss of the face with its pattern of concentric irregular circles especially was noteworthy. The patient was in desperate condition and the risk of surgical operation was considered to be great. In addition, because of the duration of the almost total motor and sensory loss, the prognosis for recovery of function was doubtful. In spite of these factors, operation seemed to offer the only help for the patient and he accepted it. Consequently, operation was performed on January 28, 1953.

Because of the extreme operative risk a consultant in anesthesia was asked to see this patient several days before operation was to be performed. Thus, the problem of anesthesia could be studied adequately. It was decided that no preoperative medication except atropine should be given. It was feared that if one of the barbiturates or morphine, either or both, were given, their action might lead to respiratory depression and arrest.

Since it was questionable that the operation would lead to improvement of the patient's breathing, tracheotomy was performed. This promised a patent airway, easily kept clear, as has been the experience with poliomyelitis patients and with those who have sustained severe head injuries. Also, tracheobronchial aspirations could be done easily by a nurse, reducing the incidence of thoracic complications. Endotracheal intubation was considered inadvisable because of the danger of edema of the vocal cords

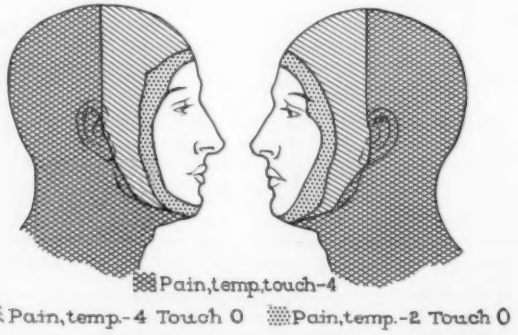

FIG. 1. Sensory pattern produced by meningioma of foramen magnum.

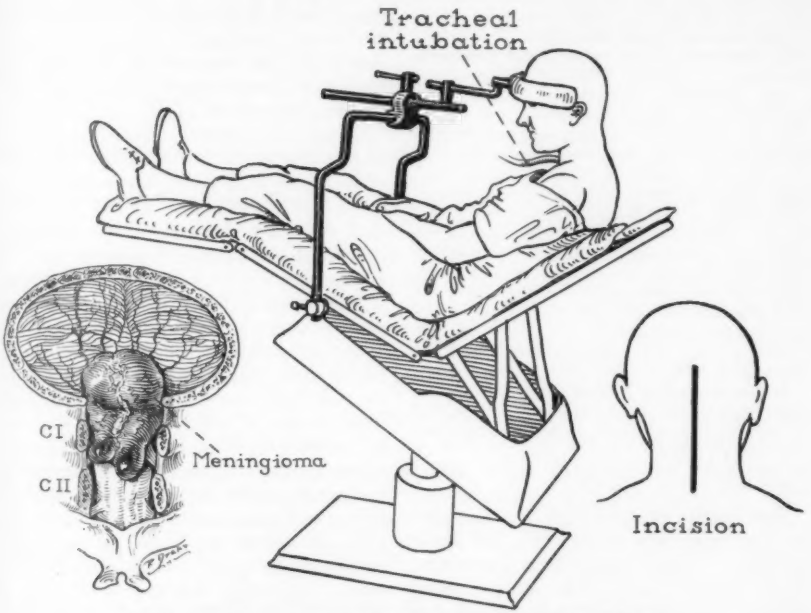

FIG. 2. Position on operating table showing tracheotomy tube in place, incision, and exposure of meningioma of foramen magnum.

and trachea if the tube were left in place for longer than 20 to 24 hours.

For anesthetic agents, thiopental sodium, nitrous oxide, and oxygen were chosen. With this combination, anesthesia could be light and oxygenation adequate. It was feared that once the patient was anesthetized, respirations would become inadequate and might even cease. What we had anticipated happened, and for 45 minutes the patient was carried totally on artificial respiration applied by exerting intermittent pressure on the rebreathing bag of the anesthesia machine. Once the dura over the foramen magnum was open, faint, spontaneous respiratory movements could be identified. Over a period of an hour and a half, first one and then another of the intercostal muscles started to function. Toward the end of the operation the diaphragm resumed its work.

To return to the plans for operation, there was a question whether the patient should be upright or prone. The prone position probably would interfere with artificial respiration. With the patient upright there is no pressure on the thorax to curtail respiratory excursions, as there is when he is prone. Moreover, the diaphragm may be splinted by the abdominal content when the patient is prone but not when he is upright. The patient's cardiovascular system can be as easily and adequately supported when he is upright as when he is prone if the Craig headrest is properly used.

The upright position was used (figure 2). First the laminae of the first, second, and third cervical vertebrae were removed. A large meningioma was found intradurally on the left side and extending through the foramen magnum. When subtotal, suboccipital craniotomy had been performed, the tumor was found to extend well up into the left cerebellopontine angle. The brainstem and cerebellum were displaced to the right. The entire tumor was removed by intracapsular enucleation and removal of the capsule. The effect on respiration has been described.

Return of function was remarkably rapid. In the afternoon of the day of operation the patient was breathing with the diaphragm and intercostal muscles and could move all four extremities. Strength of the right facial muscles was graded −2. Twenty-four hours after operation the patient could shake hands and lift

both legs off the bed. There was some return of position sense of all extremities. The patient was dismissed on the twenty-third postoperative day.

On neurologic examination at that time, strength of the right facial muscles was graded −2 and strength of the left peroneal muscle group, −1 to −2. Muscular power otherwise was normal. Superficial sensation was normal. Stereognosis, position sense, and two-point discrimination of the left hand were graded −1 to −2, while two-point discrimination of the right hand was graded −1. The gait was mildly spastic on the left. The patient could walk on heels and toes, although he had some difficulty with the left foot. He was able to hop fairly well but not normally on either foot. Muscle-stretch reflexes were mildly increased and the Babinski signs were equivocal.

Six months after the operation the patient wrote that he was normal in every way; he had no sensory loss, muscular weakness, or sphincteric defect.

COMMENT

This patient gave a history of progressive occipital headaches, sensory loss, and motor paralysis. Before quadriplegia developed, reports that the spinal fluid and the pneumoencephalogram were normal had led physicians elsewhere to consider the diagnosis of multiple sclerosis. Subsequently, motor and sensory loss was almost complete as was loss of sphincteric control. The loss of pain, temperature, and touch sense included the dermatomes supplied by C-1, C-2, and C-3. We thought this indicated that the lesion probably was at the highest cervical level. The onion-peel, concentric, dissociated sensory loss on the face has been described in association with lesions high in the cervical portion of the spinal cord. However, we also considered the strong possibility that the lesion might extend through the foramen magnum. We had no indications that it extended into the left cerebellopontine angle.

Opinion has differed concerning the segmental distribution of the descending tract of the fifth cranial nerve. According to Haymaker and Woodhall,[1] it is generally agreed that the tract descends from the pons, through the medulla, and down to the level of the upper two or three cervical segments.

Dejerine and Kraus described the segmental pattern of facial cutaneous pain and temperature sensation as having a concentric or onion-peel arrangement centering on the nose. This concept was based on lesions such as those of syringobulbia. It was considered that the portions of the face nearest the cervical dermatomes are represented in the lowest part of the spinal nucleus of the fifth cranial nerve, while the fibers from the nose and mouth terminated at the upper portion of the spinal nucleus. Other observations suggested that the distribution is similar to that of the trigeminal divisions, and that the ophthalmic division is represented in the lowest portion of the nucleus, the maxillary division in the intermediate portion, and the mandibular division in the uppermost portion.

The lesion in the case reported extended from the cerebellopontine angle to the level of C-2. Consequently, no anatomic conclusions can be made. However, on clinical examination the dissociated sensory loss followed the concentric "onion-peel" distribution.

REFERENCE

1. Haymaker, Webb, and Woodhall, Barnes: Peripheral Nerve Injuries: Principles of Diagnosis. ed. 2, Philadelphia, W. B. Saunders Company, 1953, pp. 23-30.

NEWSLETTER AMERICAN ACADEMY OF NEUROLOGY

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JANUARY, 1956

AAN Program Deadline January 7, 1956 Coming from the program committee chairman, James L. O'Leary, is the announcement that titles and 100-word abstracts of scientific presentations for the annual meeting of the AAN, to be held at the Jefferson Hotel, St. Louis (April 26-28), should be submitted on or before January 7, 1956. Titles and abstracts should be sent to Dr. James L. O'Leary, Chairman, Program Committee, 660 South Kingshighway Blvd., St. Louis 10, Missouri.... Also, titles and abstracts of approximately 200 words for scientific exhibits and demonstrations to be presented at this meeting should be forwarded on or before the same date to Dr. Benjamin Boshes, Chairman, Department of Neurology and Psychiatry, Northwestern University Medical School, 303 East Chicago Ave., Chicago 11, Ill.

New Regulations and Fee Schedules of American Board of P & N According to action taken at the October 1955 meeting, David A. Boyd, Jr., secretary-treasurer of the American Board of Psychiatry and Neurology, announces new examination requirements: all applicants who begin their residency training on or after July 1, 1956 must show that at least 24 months of their training experience was obtained in programs approved for at least two years of such training in the specialty (psychiatry and/or neurology) in which they seek certification. ... In addition, because of the increase of expenses entailed in conducting the examinations, fees will be changed as of January 1, 1956: application fee $50, examination fee $75, complete reexamination fee $75, and partial reexamination fee $50.... All inquiries relating to Board matters should be forwarded to Dr. David A. Boyd, Jr., Secretary-Treasurer, American Board of Psychiatry and Neurology, Inc., 102-110 Second Ave., S. W., Rochester, Minn.

New Diplomates in Neurology Following examinations of the American Board of Psychiatry and Neurology, held in San Francisco (Oct. 17-18), those certified in neurology are: Henry Aimar Brandt, Augusta, Ga.; Ralph Druckman, Houston; Hal C. Gregg, Santa Barbara, Calif.; William Ward Hofmann, San Francisco; William Henry Oldendorf, Los Angeles (supplementary certification); and William K. Sata, Seattle.

Epilepsy League Starts New York Meetings The annual meeting of the American League Against Epilepsy provided the "kickoff" of the perennial series of preChristmas neurologic meetings in New York. Under the guidance of A. Earl Walker (scientific program) and William F. Caveness (arrangements), activities comprised a compact program of experimental and clinical neurology, focusing on epilepsy, and a symposium on advances in medical therapy (William G. Lennox, chairman), which included reports on the therapeutic value of mysoline, P M 398, A C 695, Milontin, glutamine, and asparagine.... Russell N. DeJong delivered the presidential address.

ARNMD Meeting Centers on Aging The Association for Research in Nervous and Mental Disease held its thirty-fifth annual meeting at the Hotel Roosevelt (Dec. 9-10). "The Neurologic and Psychiatric Aspects of the Disorders of Aging" was the central topic of a comprehensive program, which included discussions on the biology of aging cells (Lansing); the life history of the neuron (Weiss); brain metabolism in relation to aging (Himwich); cerebral blood flow (Kety); psychologic aspects of aging (Lorge); the epidemiology of mental disorders in the aged (Gruenberg); genetics (Kallmann); psychopathology (Malamud); and the effects of drugs on the aging process (Lasagna). In addition, there were presentations on the neurologic changes in the aged (Macdonald Critchley); rehabilitation of neurologic disorders in the elderly (Rusk); and finally a panel discussion on the physician's contribution to the role of older persons in society, under the chairmanship of D. Ewen Cameron.... As in the past, several neurologic advisory boards and councils fringed the ARNMD and the Epilepsy League sessions in New York: Medical Advisory Boards of the Myasthenia Gravis Foundation (Dec. 9) and the National Multiple Sclerosis Society (Dec. 11); Officers and Board of Trustees of the AAN (Dec. 8); the Council of the ANA (Dec. 11); and lastly, examinations of the American Board of Psychiatry and Neurology. (Dec. 12-13).

* * * * * *

Critchley Makes Lecture Tour Arriving via Montevideo, distinguished peripatetic Macdonald Critchley of the National Hospital, Queen Square, London, recently visited the U. S. and the British West Indies on an extensive travel and lecture tour. Starting in New York on Dec. 10, he spoke on neurologic changes in the aged at the ARNMD meeting, then proceeded to Baltimore for lectures at Johns Hopkins Hospital Dec. 14; National Institute of Neurological Diseases and Blindness, Dec. 15; University of Virginia, Dec. 16; Medical College of South Carolina, Dec. 17-20; and University of Miami, Dec. 21, whence he embarked for further neurologic peregrinations in Jamaica and Trinidad.

Cerebral Palsy Group Elects New Officers

At the annual meeting of the American Academy for Cerebral Palsy in Memphis, Tenn. (Oct. 10-12), newly elected officers were: Dr. Margaret Jones, president; Dr. Nicholson J. Eastman, president-elect, and Dr. Robert A. Knight, secretary-treasurer. ... Neurologists elected to membership at this meeting were H. Houston Merritt and Pearce Bailey. The 1956 meeting will be held in Chicago; the 1957 meeting in New Orleans.

Easter Seal Foundation Announces New Research Program

The Easter Seal Research Foundation (Dr. William T. Sanger, chairman) of the National Society for Crippled Children and Adults (headquarters in Chicago) announces the initiation of a program of research grant awards for projects aimed at the investigation of problems inherent in the prevention and treatment of physical and associated disabilities. After initial screening for program emphasis by the foundation, applications for grants-in-aid under this program will be reviewed for scientific competency by designated committees of the National Academy of Sciences -- National Research Council, Washington, D. C. The final determination of research grant awards, however, will be made by the foundation. Applications should be directed toward the solution on a specific basis of one or more problems associated with physical disabilities, including their prevention. They may be oriented in basic or clinical investigations or both. For the conditions governing research awards, methods of application, and other particulars of the program, inquiries should be sent to the National Society for Crippled Children and Adults, Inc., 11 South LaSalle Street, Chicago.... Dr. Dean W. Roberts, since 1952 director of the pioneering National Commission on Chronic Illness, has been appointed executive director of the National Society, succeeding Lawrence J. Linck, who had served in this post since 1945.

* * * * * *

Deadline for Prize Essay Extended to February 1

To allow more time for the submission of manuscripts competing for the annual Woman's Auxiliary $100 prize for the best essay on a neurologic subject by an AAN junior member, the December 1 deadline for the receipt of manuscripts has been extended to February 1, 1956. To qualify, the junior member need not be the sole author of the essay but he must be the major contributor. All manuscripts must be submitted to the AAN Executive Secretary, Mrs. J. C. McKinley, 3501 East 54th Street, Minneapolis 17.... Winner of the 1954 award was John Logothetis of Minneapolis, for his essay on the proteins of the cerebrospinal fluid.

Curriculum Streamlined in Comroe Project

The pioneering program (see July 1955 Newsletter) for advance training of neurologists, under the direction of Julius H. Comroe, Jr., noted educator at the Graduate School of Medicine, University of Pennsylvania, is now divided into three trimesters

of ten weeks each, beginning in late September; one, two, or three trimesters may be taken in any academic year. The first trimester deals with the mathematics and statistics used in medical research; the second trimester with an intensive review of new technics in physics, chemistry, and physical chemistry; and the third trimester with supervised do-it-yourself training in medical teaching, writing, departmental budgeting, and administration. Throughout all three trimesters, training will be given in the critical evaluation of medical literature and in the basic sciences as they relate to one another and to clinical medicine; advance training will be offered in neurology and related specialties.... This unique program is specifically designed for physicians trained in clinical neurology (board certfied, or having satisfied the requirements for certification) or in the neurologic sciences. Preference will be given to applicants selected by the dean or department chairman for advancement in their own medical schools or teaching hospitals. A certificate will be awarded at the end of a course of study and the full academic year will satisfy, in part, the requirements of the Graduate School of Medicine for an advance degree. ... Further information and application forms may be obtained from Dr. Julius H. Comroe, Jr., Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

Briefs H. Houston Merritt has been appointed chairman of the honorary civilian consultants to the Surgeon General of the Navy.... From Lawrence C. Kolb, director of the New York State Psychiatric Institute, comes the announcement that Leon Roizin has been appointed principal research scientist, neuropathology (Sept. 16, 1955), to succeed Armando Ferraro who retired last year; Bernard C. Holland has been appointed principal research scientist, internal medicine (Nov. 1, 1955), to succeed I. Herbert Scheinberg who resigned to accept the post of associate professor of medicine at the Albert Einstein School of Medicine.... E. Jefferson Browder delivered the annual Charles A. Elsberg lecture on "Dysfunction of the Brain Consequent to Traumatic Intracranial Hemorrhage" (Nov. 15), at the New York Academy of Medicine.... Joseph Charles Yaskin, born 1891, a dynamic figure in Philadelphia neurology, noted teacher and clinician, and regular participant at Academy meetings, died on August 10, 1955.... Jonas S. Friedenwald, noted ophthalmologist and member of the NINDB Council, died November 6, 1955; his successor on the council is Derrick T. Vail of Chicago.... A clinical demonstration of patients with multiple sclerosis and the medical problem posed by this disorder was presented by Pearce Bailey, Roland P. Mackay, and Francis J. Millen, to 1,500 physicians at the Interstate Postgraduate Medical Assembly, Milwaukee (Nov. 15).

Pearce Bailey

Neurology

BOOK REVIEWS

Neuroglia: Morphology and Function

Paul Glees, M.D. 1955. Springfield, Illinois: Charles C Thomas, Publisher. 111 pages, 44 illustrations. $5.00.

THIS MONOGRAPH, a meaty one, brings the reader up to date on the structure and function of neuroglia. The presentation is orderly, the writing concise (perhaps too brief at times) and clear. Basing his discussion on a solid background of histology, the author provides a firm foundation for the emerging dynamic function of neuroglia. This is all the more important because of the movement potential known to the older anatomists and because of the rising number of contributions from chemical approaches. Indeed, it is to the histochemist that this work should have a direct appeal.

Glees utilizes the now classic classification of neuroglia into macroglia and microglia and gives thorough descriptions of the histogenesis, morphology, and metabolic considerations. The teacher will turn with special interest tc his handling of the Virchow-Robin space and the internal limiting glial membrane; he will find this a lucid exposition of a difficult topic.

The monograph presents a superb historic sketch of the early discoveries of neuroglia (Virchow 1846, Deiters 1865) and the later unfolding of further knowledge up to the present time. This is encomposed in a truly comprehensive bibiliography. Workers in the anatomy, pathology, and histochemistry of the nervous system will find a ready summary of previous work and an accessible index of the literature.

A. R. V.

Proceedings of the Third Medical Conference of Muscular Dystrophy Associations of America, Inc.

1955. New York: Muscular Dystrophy Associations of America, Inc. 324 pages. Free on request.

THESE PROCEEDINGS are divided into six symposia covering the various aspects of muscle physiology, pathology, and recent advances in knowledge of metabolic alterations in muscular dystrophy. In addition, the social aspects of the problem and clinical management of patients are considered.

Outstanding authorities on all aspects of the subject have contributed to this excellent review, and one cannot help but comment on the excellence of the presentations. For those interested in muscular dystrophy, this is certainly the most up to date review. It should be noted that all of the material appeared in the February 1955 issue of American Journal of Physical Medicine (volume 35).

Dr. Wallace Fenn, in introducing the first symposium, points out "that there are few processes in the body which have been studied so intensively as muscle contraction, and there are few cells about which so much is known as the muscle cell, and still the

problem eludes us." It is clear in muscular dystrophy that there is an inherited defect in metabolism of muscle cells. Perhaps before many more such symposiums have taken place the true cause of this unfortunate condition may have been found, and relief may be available for patients with the disease.

J. P. R.

The Pathogenesis of Poliomyelitis

Harold K. Faber, M.D. 1955. Springfield, Illinois: Charles C Thomas, Publisher. 157 pages. $5.00.

THIS SMALL VOLUME is a comprehensive and timely survey of the literature dealing with the pathogenesis of poliomyelitis. The author critically evaluates much of the more current studies in view of the results of his own investigations. Throughout this book, the author emphasizes the basic neurono-cytotropic properties of the poliomyelitis virus, and the fact that the initial invasion of the body tissues normally occurs in the peripheral nerves of the mouth and pharynx followed by a centripetal spread to the regional ganglia where multiplication of the virus occurs. The viremia in his opinion is secondary and incidental. For those interested in this subject, this small volume will prove to be a very valuable and concise review.

A. B. B.

Die Zerebralen Herdstorungen Bei Hinterhauptsverletzungen und Ihre Beurteilung

Doz. Dr. Clemens Faust. 1955. Stuttgart, Germany: Georg Thieme, Publisher. 111 pages. $3.50.

THE AUTHOR gives in a small space a clear, critical, and comprehensive review of the optical agnosias. The discussion is enlivened by the presentation of instructive cases which are illustrated by x-ray pictures and drawings. There is an adequate bibliography and a short index. The printing is excellent.

In contrast to Bay who reviewed the agnosias in 1950, Faust agrees with the older literature that the agnosias are not the result of sensory defects. Traumas of the calcarine fissure lead to cerebral asthenopia but only destruction of other parts of the occipital cortex, particularly of its basal parts, are associated with agnosias. The tendency to a restitution of function is considerable in unilateral cases. Newer methods of examination are stressed. Agnosias of the occipitoparietal region are likewise discussed.

E. G.

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ABBOTT FOUNDATION SCHOLARSHIPS

Twenty-three sons and daughters of employees of Abbott Laboratories are in college today participating in scholarships awarded by the Abbott Foundation. Alfred W. Bays, president of the Abbott Foundation and legal counsellor of Abbott Laboratories, North Chicago, Illinois, announced that a new class of 12 Abbott scholarship winners, consisting of six boys and six girls, is now in school. Eleven students from last year's class of scholarship winners are still participating in the fund.

(Continued on page 16A)

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1. Proctor, R. C.: Report on Frenquel in acute and chronic psychotic states. Presented before the Bowman Gray Medical Society, Winston-Salem, North Carolina, May 16, 1955. 2. Rinaldi, F.; Rudy, L. H., and Himwich, H. E.: The use of Frenquel in the treatment of disturbed patients and psychoses of long duration, Am. J. Psychiat., in press. 3. Fabing, H. D.: Frenquel, a blocking agent against experimental LSD-25 and mescaline psychosis, Neurology 5:319, 1955. 4. Fabing, H. D.: New blocking agent against the development of LSD-25 psychosis, Science 121:208, 1955.

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(Continued from page 14A)

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Scholarship recipients are selected each year by a committee which consists of the president of the Foundation, an employee of Abbott Laboratories, and four prominent Chicago educators. In making its selections, the committee weighs each applicant's scholastic achievement, financial circumstances, and his participation in worthwhile extracurricular activities.

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